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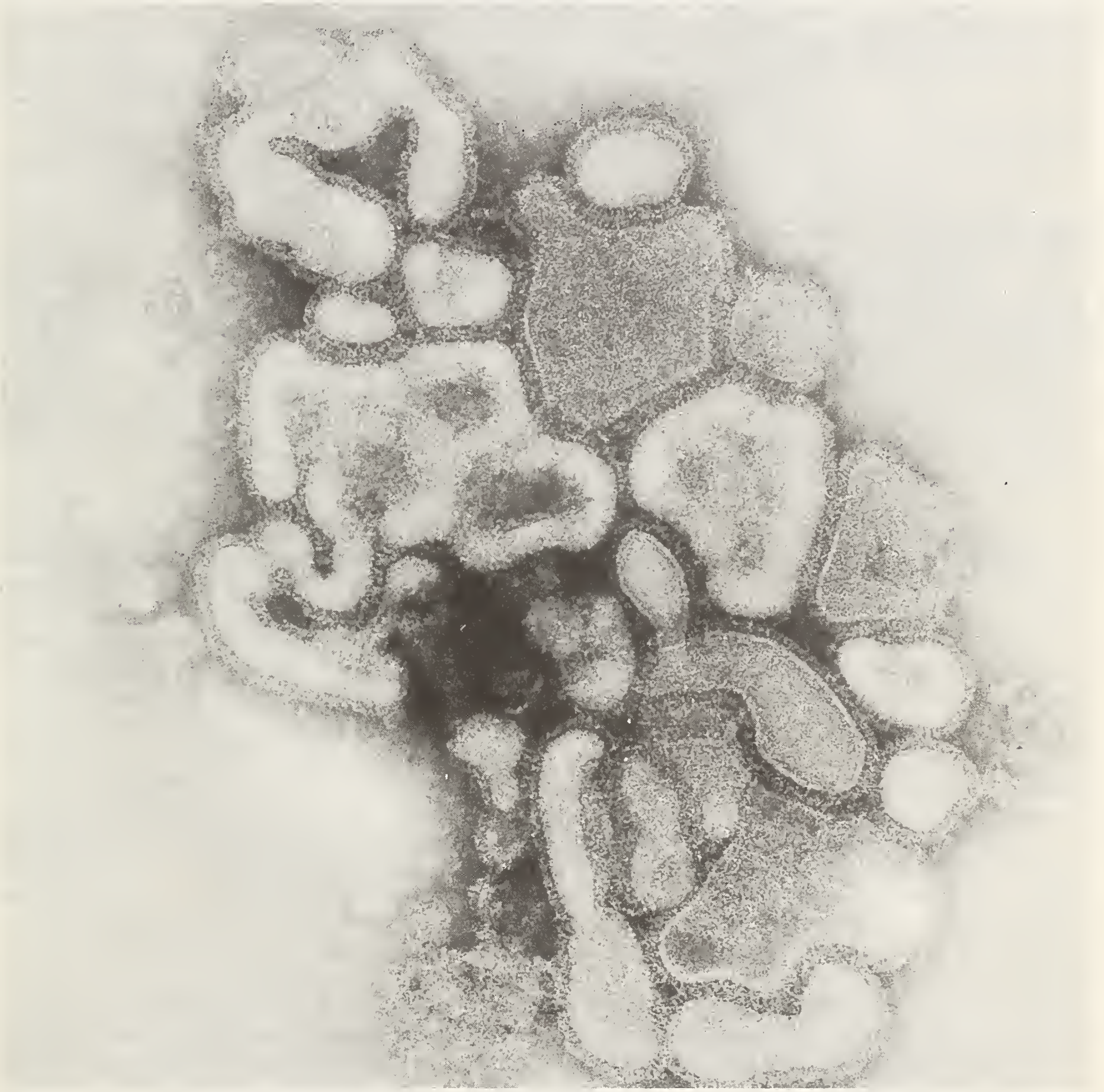
NEWS&FEATURES FROM NIH

PORTFOLIO – NIAID Influenza Research Center

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE■Public Health Service■National Institutes of Health■Office of Information■Bethesda, Maryland 20014



Cover photo: *Influenza A/New Jersey is shown at a magnification of 151,200.*

JANUARY 1978

NIH Portfolio on the NIAID Influenza Research Center

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Introduction:

Influenza has been called man's last great plague. It is the focus of a unique multidisciplinary research center supported by NIH's National Institute of Allergy and Infectious Diseases. In 1974, the Baylor College of Medicine in Houston, Texas received a $2.8 million, five-year contract from the NIAID to set up the nation's only comprehensive influenza research center. Now, in its fourth year of operation, the Influenza Research Center continues to conduct a diverse program aimed at answering many of the puzzling questions surrounding this all too familiar disease.

Since predicting and preventing flu is a major public health problem, it is being attacked by Baylor through studies in epidemiology, immunology, pathology, virology, vaccine evaluation and chemotherapy. Run by a staff of approximately 30 health professionals, the Center carries out research programs involving various population groups -- from the very young to the very old -- under observation for extended periods. Information obtained from these investigations -- which may last as long as 10 years -- should provide the basis for more effective influenza control.

Epidemiology:

Baylor researchers are especially interested in studying the various ecologic expressions of influenza in the community. For instance, they hope to identify high risk groups, to learn more about how the virus is spread, to assess the economic and social effects of the disease, and to detect early signs of influenza activity in a community.

Early identification of a flu outbreak is extremely difficult. Every 10 years or so a new influenza A virus appears, producing a pandemic (world-wide epidemic), and almost every year lesser variants of both the A and B influenza viruses cause smaller-scale epidemics. These usually appear quickly, leaving little time for mass production and distribution of new vaccines.

For the past three years, continuous surveillance of the Houston population has been carried out by Center staff members collaborating with community hospitals, neighborhood health centers and private physicians. Samples of throat washings and other upper respiratory tract fluids are taken from individuals who report to these facilities with flu-like symptoms. These specimens are then cultured for influenza viruses. Although other factors indicative of influenza activity, such as increased school and work absenteeism and hospital admissions, are studied, isolating influenza virus from an increasing number of people appears to be the clearest early sign of an impending influenza epidemic.

To date, the flu researchers have followed three epidemics in the Houston area, noticing what they refer to as the "herald wave" effect, where a few cases of influenza appear several months before a major outbreak. In addition, data collected from a recent influenza B epidemic suggest that outbreaks of flu occurring between pandemics produce a significant social and economic impact on the community. For example, as much as 11 percent of the Houston population contracted influenza B in 1976.

Tracking influenza infections in families has already revealed some interesting information on transmission of the flu, as well as demonstrating the severity of the disease in children. In the 38 families studied during an epidemic, those with school-aged children -- 5 to 19 years old -- had the highest rates of infections. Thus, this age group was found to be the single most important factor in the introduction and early spread of the disease. In addition, surveillance of children hospitalized with respiratory viral infections indicated that influenza is a serious pediatric problem deserving more widespread recognition.

Vaccine Evaluation:

Protection offered by inactivated influenza vaccines is confined to the strain or strains of the virus prevalent in the community at the time. In addition, the mild adverse reactions to these vaccines may limit their acceptability in certain populations. At the Baylor Center, evaluation of influenza vaccines is an extensive ongoing effort to study and improve vaccines now in use and to develop new, more effective ones. In the past year alone, more than 1,100 people of all ages in the Houston area participated in eight influenza vaccine trials.

In 1976, the Influenza Research Center contributed to the National Influenza Immunization Program through a cooperative project involving the NIAID, the Bureau of Biologics and the Center for Disease Control. These studies were aimed at determining acceptable doses of swine flu (A/NJ/76) vaccine for normal and high risk adults. Both monovalent and bivalent vaccine (A/NJ/76) and (A/VIC/75) were studied, as well as the immunizing effects of various routes of administration.

More information is needed on the use of influenza vaccine in children, who appear more susceptible to adverse reactions than adults, and are less likely to develop protective levels of immunity at tolerable doses. To alleviate these problems, the influenza researchers are testing the safety and effectiveness of HANAflu vaccines -- purified versions of influenza vaccines containing only the antigens necessary to induce immunity. Results obtained from this work indicate the need for further evaluation of both commercial and investigational vaccines in high risk and normal children.

The testing of live attenuated virus vaccines is being vigorously pursued by the influenza researchers in the hope that they will produce longer lasting immunity than the present killed virus vaccines. In addition, live virus vaccines may decrease the incidence of a poorly understood paralysis (the Guillain-Barre syndrome), a condition which was rarely observed with the use of killed virus vaccines.

One approach to the development of attenuated influenza vaccines has been the use of temperature sensitive (ts) mutants of the influenza A virus. Intramural scientists of the NIAID have developed a series of these vaccines, which are currently under investigation at the Influenza Center. The vaccines are prepared from viruses that are treated chemically and selected for their ability to grow in the cooler temperatures of the upper respiratory tract, but not in the lungs, where they can cause serious illness. In tests with adults, some of the ts-virus vaccines -- although producing effective antibody levels -- were shown to retain their ability to cause a mild form of influenza. Another approach is the use of vaccines prepared from cold-adapted recombinant strains, developed at the University of Michigan and also under investigation at the Influenza Research Center. In a recent study, the cold-adapted-vaccines -- when administered intranasally -- appeared to induce adequate immunity with little or no side effects. Researchers at Baylor continue to evaluate both the temperature sensitive and cold-adapted vaccines for their effectiveness and safety.

Immunologic Studies:

Understanding the body's natural defense mechanisms against influenza is essential to the development of effective approaches to control. Thus, the role of the immune response during flu infections, particularly cell-mediated immunity, is the subject of intensive investigations at the Baylor Center. The scientists have found that when blood samples taken from normal adults during a flu infection are mixed with influenza-infected hamster cells, the lymphocytes induce general cell-killing reactions observed in other viral infections. The significance of these reactions -- thought to be important in the recovery process -- remains to be determined. In other studies with human volunteers, the effects of cold-adapted vaccines on normal immune responses are being looked at with a view toward eventually understanding naturally induced immunity.

Baylor immunologists have more recently developed a mouse model system for investigating the cell-mediated response. Work by these scientists suggests that these responses may be a "double-edged" sword, important in resistance, but also important in the development of influenzal complications, such as pneumonia. Further projects with the mouse model will attempt to discover why infections with one influenza virus may lead to more severe disease during a second infection with a different influenza virus.

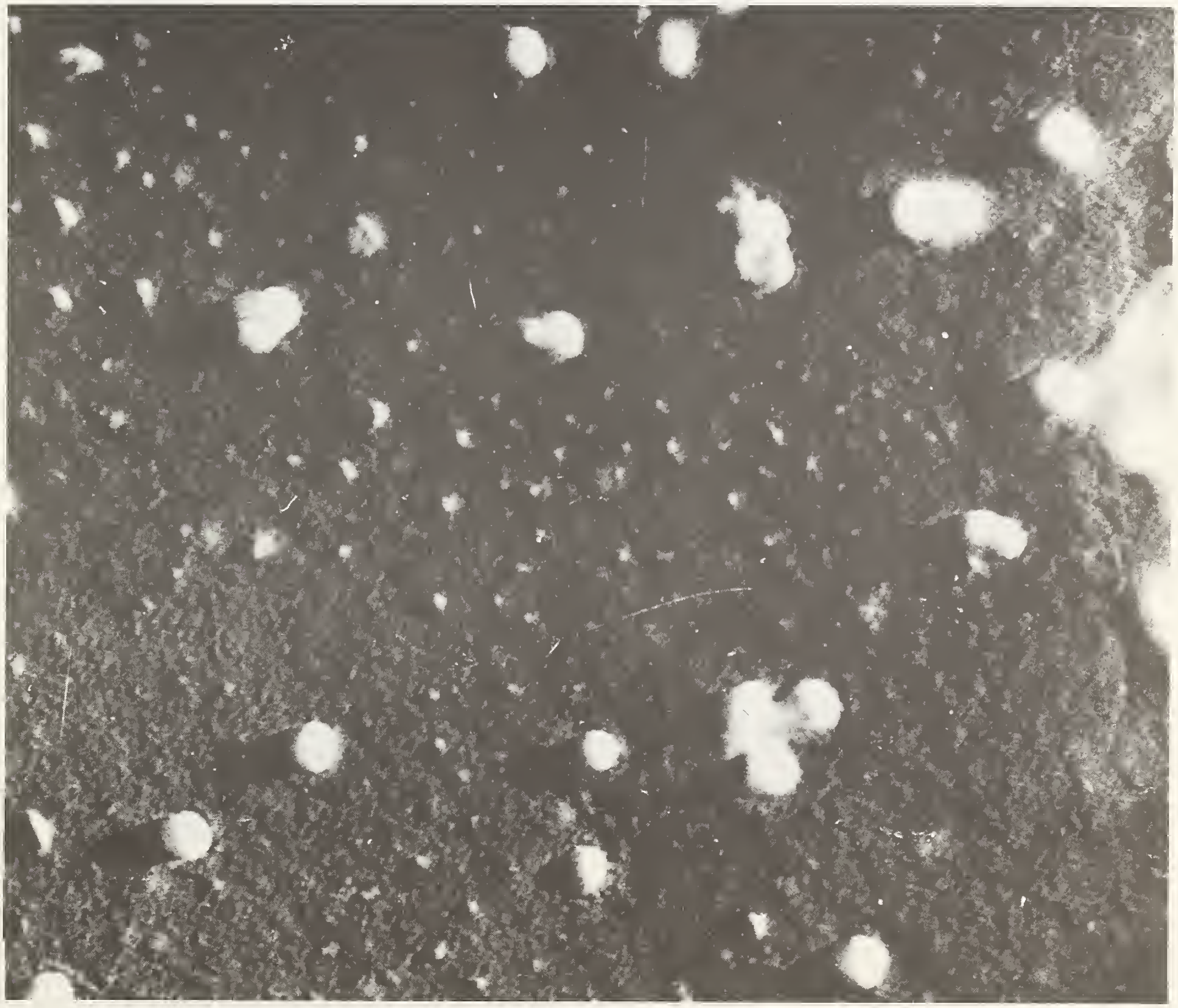
Improved Diagnostic Techniques:

The development of a radiolabeling technique for accurately detecting influenza viral antigens has permitted investigators at the Influenza Center to design experiments aimed at understanding antigenic variability among the influenza viruses. This relatively new investigational tool may prove to be a more rapid and reliable method of diagnosing influenza infections than presently used techniques. Efforts such as these continue to develop and refine similar methodologies, integral to influenza research.

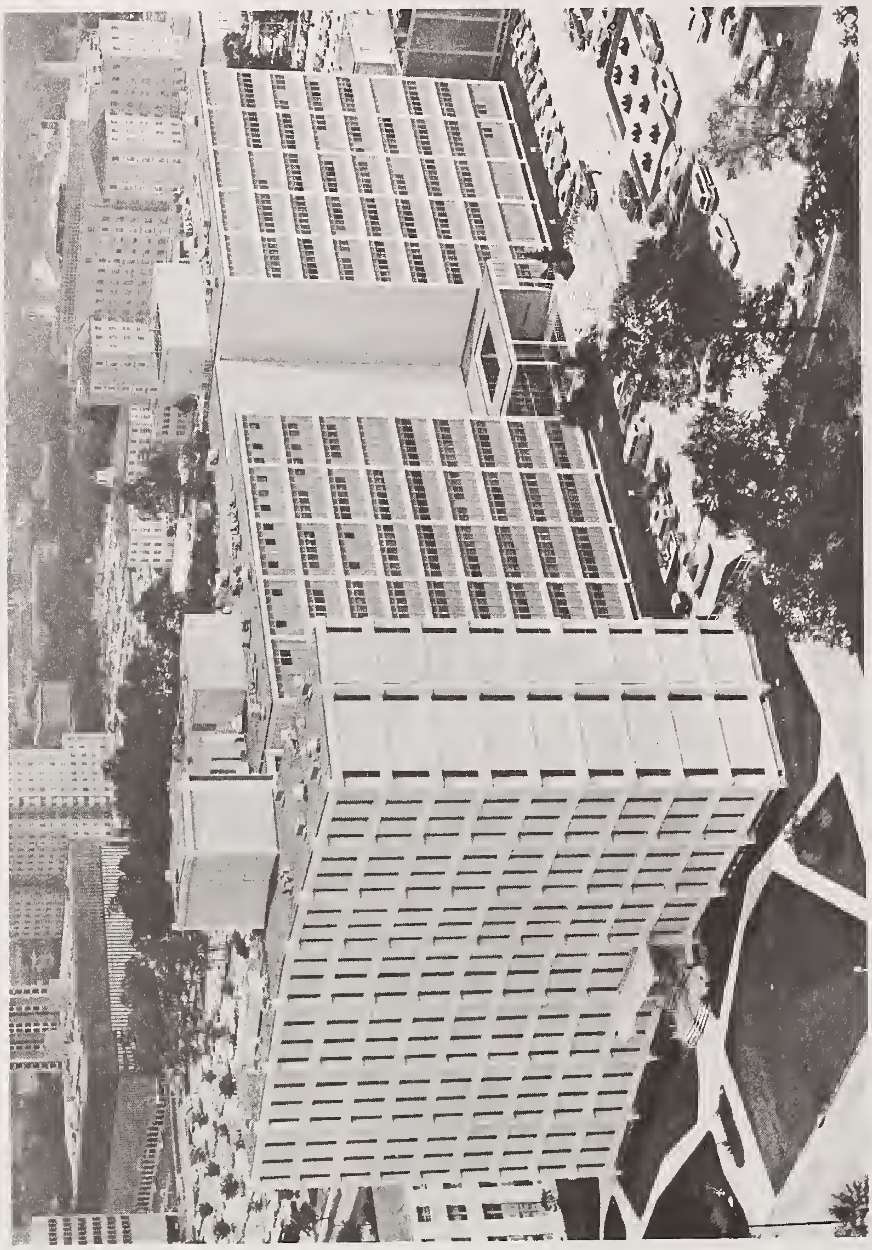
Antiviral Compounds:

Influenza pneumonia -- a serious complication of flu -- is an illness that can be life-threatening to high risk groups. Baylor clinicians are evaluating antiviral compounds, such as amantadine hydrochloride, in elderly populations, as potential prophylactics, used either alone or in combination with vaccines. Already established as a useful prophylactic drug, amantadine is also being evaluated in the treatment of influenza, as is rimantadine, a derivative of amantadine.

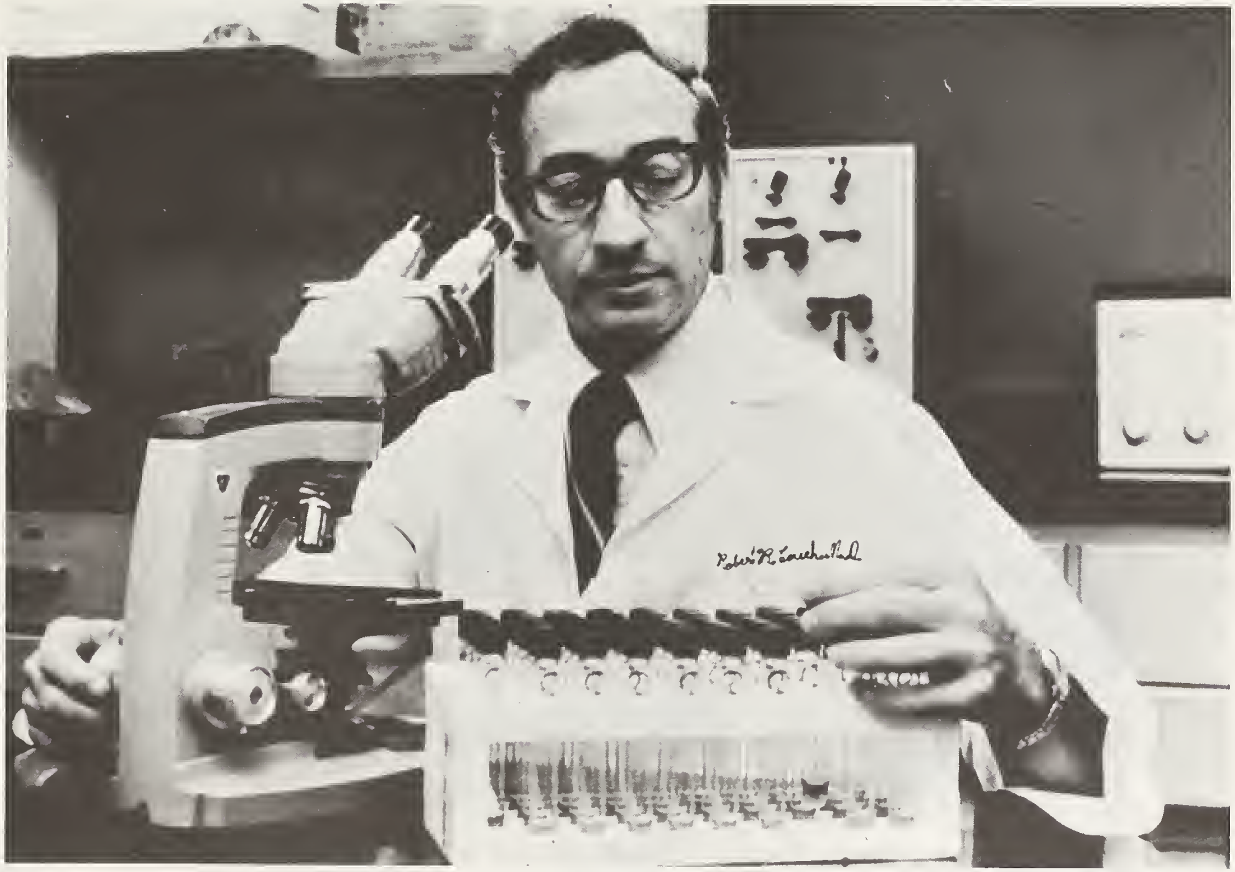
Comprehensive research programs, such as the one carried out at the Baylor Influenza Research Center, are a new approach to understanding and controlling major illnesses. Only through such efforts will mankind's "last great plague" be conquered.



Most viruses show this "cottonball" silhouette under the electron microscope. These influenza viruses are growing on a membrane.

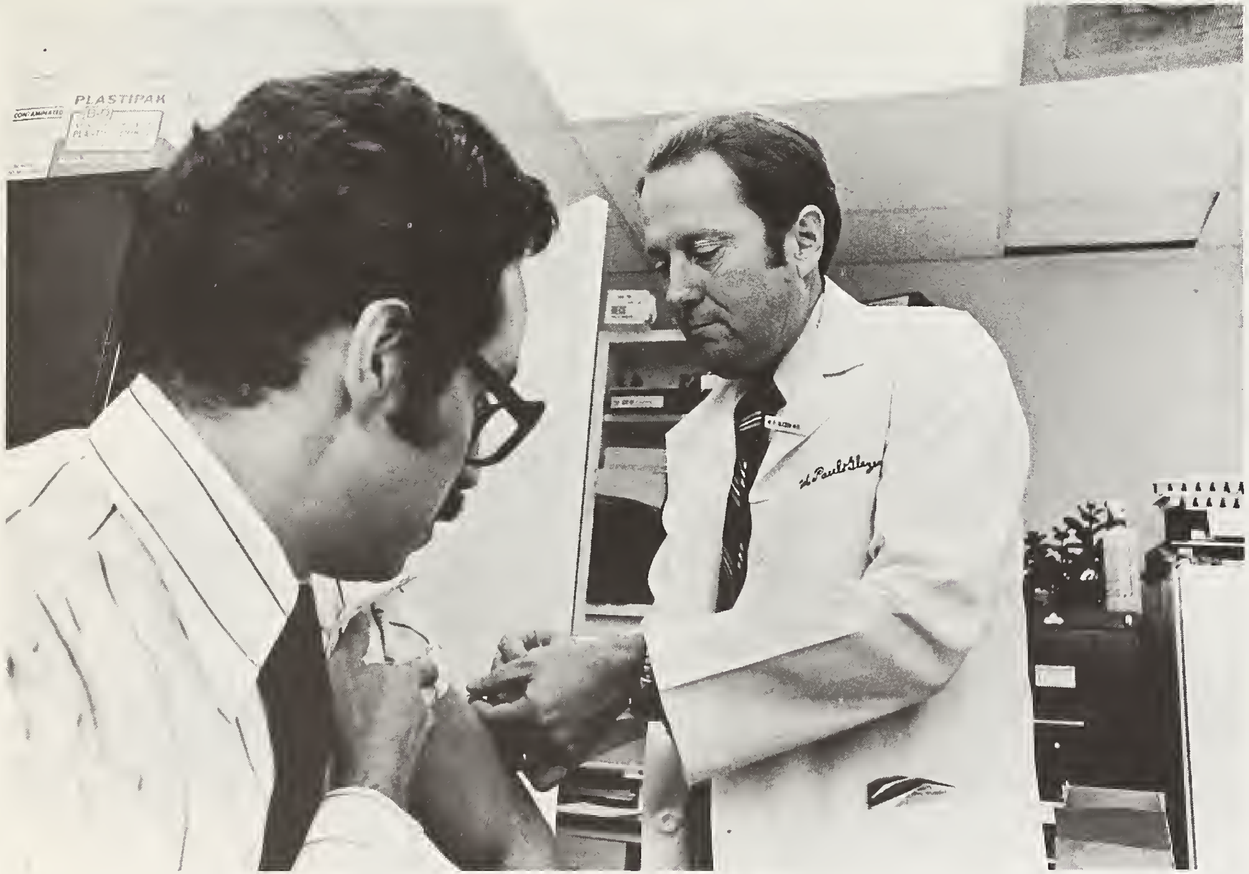


The Influenza Research Center is located on the campus of Baylor's College of Medicine in Houston, Texas. Extablished in 1900, the College is the only private medical school in Texas and the focus of the Texas Medical Center. (NIH Photo # TX 1)



Since its inception in 1974, the NIAID-funded Influenza Research Center has been under the direction of Robert B. Couch, M.D., professor of microbiology, immunology and medicine at the Baylor College of Medicine. Together with a team of investigators, Dr. Couch has set up a broad-spectrum research program designed to clarify the complex nature of influenza. The program covers such diverse fields as epidemiology, immunology, and pathology as well as vaccine evaluation and testing of potential antivirals. (NIH Photo #TX 2)

Drs. Vernon Knight, Robert Couch and Julius Kasel, scientists at the Influenza Research Center, evaluate an influenza test. Developing and refining laboratory tests and techniques is an important part of the Baylor flu program. Better methods of testing for influenza infection will improve diagnosis as well as contributing to a more thorough understanding of the disease. (NIH Photo #TX 3)



The Influenza Research Center plays an active role in inoculating members of the community, since the Center is responsible for medical services in the Harris County (Houston) Hospital District. Local pediatrician (left), Dr. Abel Paredes receives his annual influenza immunization from Dr. W. Paul Glezen, associate professor, microbiology, immunology, and pediatrics at the Baylor College of Medicine and professional staff member of the Influenza Research Center. (NIH Photo # TX 4)

Baylor employees, students, and staff receive influenza vaccinations at the Baylor Family Practice Center. At the Influenza Research Center, vaccine evaluation is carried out in different population groups to improve vaccine safety and effectiveness. (NIH Photo # TX 5)

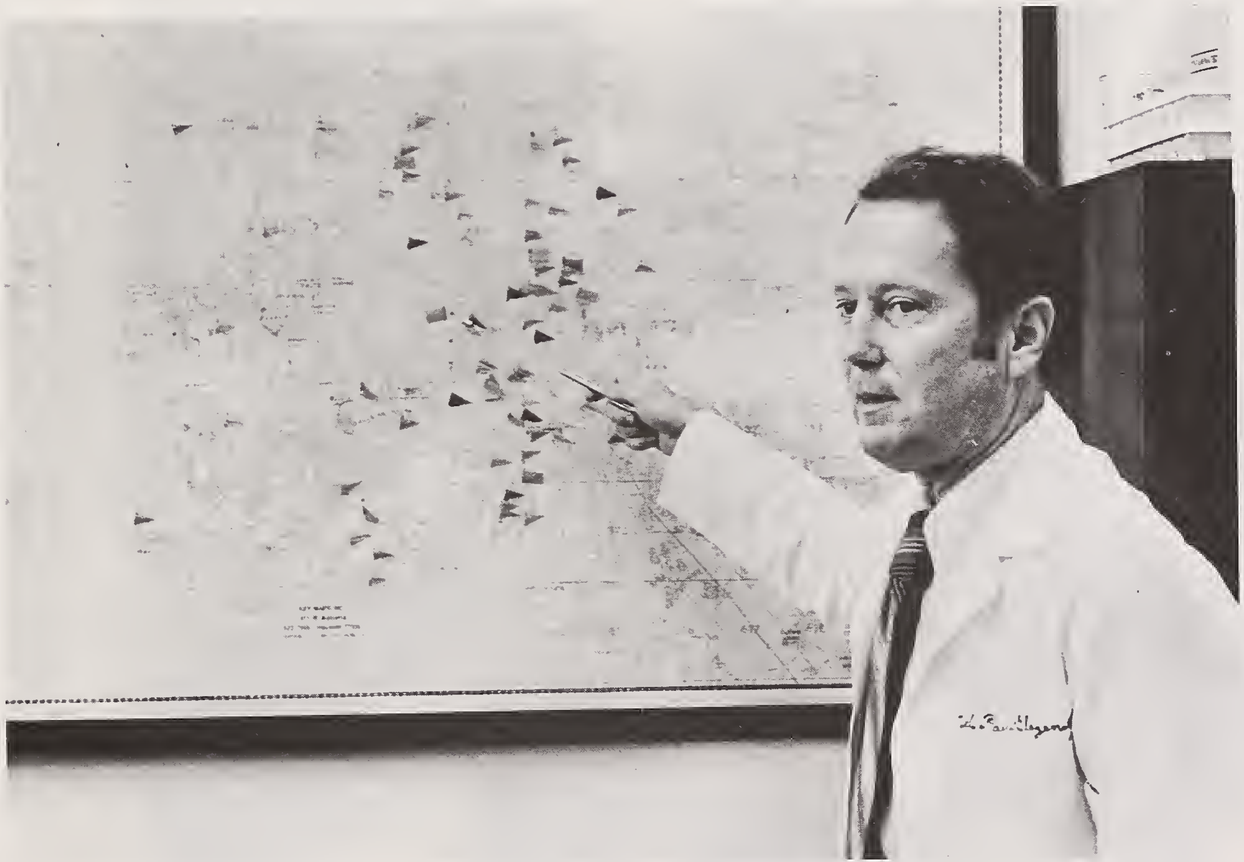
Barbara Baxter, a research associate with the Influenza Research Center prepares embryonated eggs for influenza virus isolation. Fertilized eggs are used because chick embryos are susceptible to influenza virus infection and large amounts of virus can be grown in their tissues. The process of isolation takes 2-3 days and sometimes longer. Specimens are obtained from patients usually in the form of throat swabs or nasal samples. These specimens are then inoculated into the chick embryo through a pinprick hole in the egg shell. The hole is sealed and the eggs are returned to the incubator for 24-48 hours. If virus is present in the original specimen, the chick embryo will die and material can be removed from the embryo that contains the virus. This material, allantoic fluid, can then be used for virus identification and analysis. (NIH Photo # TX 6)

Research technician, Mary Ann Hrovat, puts fresh media in tissue culture tubes Influenza viruses are sometimes propagated in tissue culture in addition to embryonated eggs. In fact, influenza B viruses seem to grow better in monkey kidney cell cultures than in fertilized eggs. In a typical culture, the cells grow in monolayers that can be easily observed for viral growth. (NIH Photo #TX 7)

Rhonda Zimmerman (foreground) and Uzi Sitzer, research technicians, change the media on tissue culture cells used for influenza isolation. The media contains a red acid-base indicator that changes color when toxic cellular byproducts build up in the culture. These byproducts are the result of cell growth, which is maintained optimally in a ph-balanced solution.
(NIH Photo # TX 8)

Gertrude Burnside, a laboratory technician at the Baylor College of Medicine Influenza Research Center, examines a cell culture under the microscope. Cells that exhibit cytopathic cell-killing effects, such as odd-shapes, are thought to be the victims of viral replication. After examination, these cells are removed from the culture and inoculated into a fresh cell line to which guinea pig erythrocytes have been added. Viral infection is confirmed if the erythrocytes clump together with the defective cells. This phenomena, known as hemagglutination, is a common test for many human viruses. (NIH Photo # TX 9)

*. Thomas Cate, associate professor, microbiology, immunology, and medicine,
aided by Shellie Scott, a research technician, as he injects influenza
tigens into a mouse tail vein for immunological studies. Dr. Cate and other
ylor scientists have developed the mouse model for influenza, which has proven
uable in investigating the role of the immune response in this disease. So
, the Baylor studies suggest that the cellular immune response of mice,
diated by T and B lymphocytes, is important in the disease process as well
in recovery. (NIH Photo #TX 10)*



Intensive surveillance for influenza infection in Houston is undertaken by Dr. Paul W. Glezen, Baylor College of Medicine associate professor of microgiology, immunology, and pediatrics. Working with the Baylor Influenza Research Center staff, Dr. Glezen is trying to determine the nature and extent of influenzal illness in the community. Illness is documented by virus isolation and by monitoring school and work absenteeism and hospital admissions. Local clinics, hospital emergency rooms, and general practitioners contribute to this effort. (NIH Photo #TX-

NEWS&FEATURES FROM NIH

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February 1978

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DATA ABOUT LUNG DISEASES CAN BE DISPLAYED BY COMPUTER

Recent advances in computer science and nuclear medicine are enabling National Institutes of Health physicians to demonstrate graphically and visually the functioning of specific regions of diseased lung in patients affected by pulmonary fibrosis, emphysema, and other lung diseases.

Bruce R. Line, M.D., of NIH's Division of Computer Research and Technology, reported October 27, 1977, at a NIH Science Writers Seminar that three types of pulmonary information can now be displayed by computer images. They are (1) the adequacy of the patient's blood supply and air supply in any given region of the lung; (2) the ratio of the transport of air and blood to lung tissues (this helps assess the capacity of the patient's lung to provide oxygen to the blood and remove carbon dioxide); and (3) the concentration of oxygen and carbon dioxide in both the air and blood of any lung region, as estimated by mathematical modeling techniques.

The lung works best when air enters and leaves the lung easily, and when the air and blood come into contact across the alveolar membrane of the lung in uniform proportions throughout the lung. The adverse effects of pulmonary disease can arise from changes in the ratio of ventilation (V) to circulation or perfusion (P) in regions of the lung as well as overall decrease in V or P.

In the NIH studies, conducted jointly by scientists of the Division of Computer Research and Technology, the Clinical Center, and the National Heart, Lung, and Blood Institute, the patient's air supply and pulmonary blood are tagged with minute amounts of short-lived radioactive tracers.

The air supply is tagged with radioactive xenon as the patient breathes

(more)

LUNG DISEASES (CONT'D)

xenon-containing air orally from a spirometer. Pulmonary blood is labelled by injection into a vein of ^{99m}technetium macro aggregated albumin. The labelled albumin particles are larger in diameter than pulmonary capillaries and are temporarily trapped there during the measurement of tracer activity.

Gamma rays emitted from the tracers in both air and blood in the patient's lung are then measured during respiration by a gamma camera placed behind the patient's chair. The tracer activity is visualized and measured by scintigraphic imaging equipment linked to the gamma camera.

For more sophisticated measurements, the scintigraphic information is transmitted to computers programmed by the Nuclear Medicine Department of the NIH Clinical Center. The computer then constructs pictures showing changes in the lung's air and blood spaces. Using the NIH approach, the diseased pulmonary area is indicated by a regional abnormality in air supply, blood supply, V/P ratio, or oxygen/carbon dioxide exchange.

Dr. Line noted that the new techniques described can visualize 1200 to 1500 regions in the lung, and identify regionally any diseased area. The research technique also enables him to determine whether the problem is related to blood flow or air flow.

In June 1977, he presented data on seven patients with idiopathic pulmonary fibrosis at the meeting of the Society of Nuclear Medicine in Chicago. Data on the patients' pulmonary function were presented both scintigraphically and with mathematical curves. For the latter, Dr. Line and his NIH colleagues developed a mathematical technique for determining the rate of aeration of the lung and have produced images which estimate the regional carbon dioxide

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LUNG DISEASES (CONT'D)

and oxygen content of the lung based on a mathematical model of gas exchange.

Dr. Line emphasized that these advances in pulmonary scintigraphy and related aspects of nuclear medicine are based on the pioneering efforts of Drs. George Taplin at UCLA, Henry Wagner at Johns Hopkins Medical Institutions, and Kenneth Moser at the University of California.

The NIH approach in applying mathematical modeling procedures to lung studies owes much to earlier work by Dr. G. Richard Kelman of the University of Leeds, England, and Drs. John B. West and Peter D. Wagner at the University of California in La Jolla.

#

VARIOUS DIAGNOSTIC METHODS FOR LUNG CANCER ARE EVALUATED

The status of early diagnostic methods and therapy in bronchogenic carcinoma was reported October 27, 1977, by Dr. John D. Minna, Chief of the NCI-VA Medical Oncology Branch, Washington, D.C. He spoke at an NIH Science Writers Seminar. Despite some advances, 80 percent of the 102,000 persons developing lung cancer in the U.S. this year will be dead within two years of diagnosis and 50 percent will die within six months of diagnosis.

Dr. Minna said that lung cancer is still the most commonly lethal cancer among U.S. men and the incidence of this disease in women is increasing at an alarming rate. Consequently it can be predicted that there will be annual increases in the number of newly diagnosed cases of this disease over the next several years. The role of cigarette smoking as the principal causative factor for the majority of lung cancer patients cannot be overemphasized.

Early diagnosis of lung cancer is essential since surgery and radiotherapy may offer curative treatment for those lung cancer patients with early-stage disease. Advances in methodologies for early diagnosis were reported by Dr. Minna. Early diagnosis can be achieved by annual chest X-ray examination of high-risk persons, with cytologic examination of deep-cough sputum specimens at four-month intervals.

Malignant cells may be found in the sputum before abnormalities are noted on the chest X-ray examination. When malignant cells are detected, fiberoptic bronchoscopy is performed to determine the site of origin of the tumor. Preliminary results from screening programs at Johns Hopkins University, Mayo Clinic, and Memorial Sloan-Kettering Cancer Center suggest that chest X-rays and sputum cytology are complementary, aiding in detecting early-stage

(more)

LUNG CANCER (CONT'D)

disease in different lung cancer types.

Lung cancer consists of four major histologic sub-types: epidermoid (squamous cell) carcinoma, adenocarcinoma, small cell anaplastic (including oat cell) carcinoma, and large cell anaplastic tumors. Dr. Minna stressed that a biopsy specimen of the tumor be examined by a pathologist experienced in lung cancer to differentiate small cell carcinoma from the other histologies. Small cell carcinoma usually disseminates early and generally cannot be surgically removed. For this cell type, which occurs in about one in five lung cancer cases, chemotherapy alone or with radiation therapy constitutes optimal treatment.

Dr. Minna summarized recent studies using radiotherapy and/or chemotherapy at more than ten medical centers and including 563 small cell lung cancer patients. Eighty percent of patients had tumor shrinkage, and 40 percent had temporary, complete disappearance of the tumor. While previously the expected median survival was less than three months, in these pateints the median survival is approaching one year. Even more important, a small number of patients are remaining disease-free for several years after completion of all therapy.

At the National Cancer Institute three studies have been conducted on this disease, at the NCI-VA Medical Oncology Branch (led by Dr. Martin Cohen), Radiation Oncology Branch (led by Dr. Ralph E. Johnson) and NCI's Baltimore Cancer Research Center (led by Dr. Peter Wiernik). Over 170 patients have been treated in these NCI programs with complex regimens involving intensive treatment with various combinations of chemotherapy, radiotherapy, and immunotherapy. Over 50 percent of all patients experienced a complete but temporary disappearance of clinically detectable tumor.

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LUNG CANCER (CONT'D)

The median survival for the 170+ patients is over one year. In late-stage disease, a median survival of 14 months was achieved; in early-stage disease, median survivals ranged from 18 to 20 months.

Dr. Minna said the NCI investigators are encouraged by the results among patients with earlier stage disease, more than 50 of whom (over one-third) survive longer than two years. These patients feel well and are active during most of this time. Dr. Minna indicated these results represent a group effort by NCI physicians including Drs. Harmar Brereton, Paul Bunn, Robert Esterhay, Byron Fossieck, Harry Kent, Daniel Ihde, Joseph Aisner, and Mary Matthews.

Treatment of patients with advanced, non-small cell cancer is discouraging. However, within the past two years several regimens of chemotherapy alone or chemotherapy combined with radiation therapy have produced objective tumor shrinkage in 30 to 40 percent of treated patients. These patients usually live several months longer than unresponsive patients. In addition, the quality of life also improves for responding patients. Active drugs in non-small cell cancer include Adriamycin, cyclophosphamide, CCNU, methotrexate, 5FU, procarbazine and a platinum compound, cis-diamminedichloroplatinum 2.

Dr. Minna emphasized that treatment of inoperable lung cancer, especially small cell carcinoma, involves intensive, highly toxic treatment programs. Such treatment is best given by an experienced medical oncologist or by physicians at a cancer center.

In addition, Dr. Minna reported advances in studying the biology of lung cancer. Dr. Adi Gazdar and colleagues at the NCI-VA unit have been able to

(more)

LUNG CANCER (CONT'D)

grow human small cell carcinomas is tissue culture and in immune deficient (nude) mice. Studies are aimed at determining growth factors for these human lung cancer cells, and the response of the cells to various treatments in the laboratory.

#

ENVIRONMENTAL FACTORS ARE LINKED TO LUNG DISEASE

At a Science Writers Seminar on human lung disease held at the National Institutes of Health on October 27, 1977, Dr. Ronald G. Crystal, Chief of the Pulmonary Branch, of NIH's National Heart, Lung, and Blood Institute presented a broad overview of the problem of pulmonary fibrosis and its impact on Americans.

Dr. Crystal summarized occupational and environmental factors known to be linked to fibrotic lung disease, and described other disorders where pulmonary fibrosis plays a role but its origin is unknown.

The fibrotic lung disease (scarring of the air sacs of the lung) represent approximately 15 percent of all non-infectious lung disorders. These are important disorders; many are fatal and attack individuals in their prime. Although many (approximately 130) of the fibrotic disorders are due to a known agent which causes lung injury, in many patients the etiology is unknown.

Patients with fibrotic lung disease first note something wrong with their lungs when they experience shortness of breath performing common daily tasks (e.g., running to catch a bus, doing housework). On physical examination, their physician usually finds a crackling sound (rales) with respiration, a generalized infiltrative pattern on the chest X-ray, and reduced lung volumes on lung function testing (e.g., the patient can only take in small amounts of air with a full breath).

A major area of investigation of the Pulmonary Branch, National Heart, Lung, and Blood Institute is to investigate the fibrotic lung disorders at the molecular level and to bring these findings to the bedside as rapidly as possible. To do so, Dr. Crystal and his colleagues have focused on two major

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ENVIRONMENTAL FACTORS (CONT'D)

aspects of the fibrotic lung disorders: (1) the fibrosis itself; and (2) the abnormal inflammatory and immune processes which cause the fibrosis.

The major constituent of fibrosis tissue is the macromolecule collagen, a long, tough molecule that resists stretching. Quantitative evaluation of the fibrosis of idiopathic pulmonary fibrosis (IPF; lung fibrosis of unknown cause) has demonstrated that although the collagen in lung is present in normal amounts, it is deranged in type, form, and location. Since collagen is such a tough molecule, a special enzyme, called collagenase, is necessary to initiate its derangement. Evaluation of the quantities of collagenase in the lower respiratory tract of patients with IPF has demonstrated that they have excess amounts of this enzyme compared to normal persons.

One source of collagenase is the white blood cells which are drawn to areas of chronic inflammation such as that found in the lung in IPF. Evaluation of the cells of the lower respiratory tract of these patients have demonstrated that they have excess numbers of white blood cells. Since the amount of inflammation present seems to be a "trigger" to induce progressive derangement of lung collagen, the clinician caring for these patients needs to have techniques to quantitate lung inflammation.

Toward this end, two procedures have been developed: (1) lavage ("washing out") of the lung with small amounts of fluid poured through a flexible fiberoptic bronchoscope; and (2) nuclear scanning with ^{67}gallium. The latter procedure, developed in collaboration with the Nuclear Medicine Department of the NIH's Clinical Center and the Laboratory of Applied Sciences of NIH's Division of Computer Research and Technology, has enabled direct, non-invasive

(more)

quantitation of the relative number of inflammatory cells present in the lungs of these patients.

Dr. Crystal said that as these studies have progressed, it has become apparent that it will be very difficult to treat the fibrosis itself, but possible to halt the inflammatory and immune processes which lead to the fibrosis. Thus, the therapy of IPF is being directed toward medications which may inhibit the abnormal inflammatory and immune processes that are present in these patients. As one approach to the therapy of these patients, the Pulmonary Branch has undertaken long-term study of the effectiveness of anti-inflammatory and anti-immune type medications in the treatment of IPF.

#

GOOD PROGRESS IS REPORTED AGAINST HODGKIN'S DISEASE

There is now reasonable hope that Hodgkin's Disease, which was once considered universally fatal, can be cured with minimum side effects, perhaps years before the cause of the disease is known and it is possible to prevent it, according to Dr. Vincent T. DeVita, Jr., of NIH's National Cancer Institute.

Dr. DeVita, Director of the NCI Division of Cancer Treatment, said that gains in both the treatment and understanding of the natural history of Hodgkin's Disease now make it possible to devise complete treatment experiments to improve on the presently "crude but effective" methods used to cure this disease.

It is now possible to cure more than 70 percent of all patients with Hodgkin's Disease, but treatment methods are toxic and a significant number of patients, particularly those with advanced disease, currently suffer relapses which can be ultimately fatal.

Dr. DeVita, who is internationally regarded for his pioneering work in the development of a four-drug chemical treatment (called MOPP) which has cured significant numbers of patients with far advanced Hodgkin's Disease, made his remarks on September 30, 1977, at the National Conference on the Lymphomas and Leukemias. The meeting was sponsored by the National Cancer Institute and the American Cancer Society.

The first progress in treating Hodgkin's Disease with chemicals (chemotherapy) occurred in the 1940's with the discovery that a drug called Nitrogen Mustard, which was derived from a war gas, had an initial killing effect against the tumor cells. This caused great excitement but all of the patients treated with the drug relapsed within weeks and as a result a feeling of dejection and skepticism about the usefulness of drug therapy developed within the medical

(more)

HODGKIN'S DISEASE (CONT'D)

community. Although this pessimistic climate continued into the 1960's, other effective drugs (the vinca alkaloids, corticosteroids and methylhydrazines) were developed during the same years. At the same time new knowledge was generated about how tumor cells are killed and the principles of combining different drugs (combination chemotherapy) began the long developmental march that led to the ability to cure at least 11 otherwise fatal cancers with chemica alone by the 1970s.

These early historical efforts led to a marked increase in response rates of patients with Hodgkin's Disease. Before the development of chemotherapy, the use of X-rays (radiotherapy) was the only effective method of treatment, but it was incapable of producing cures with far advanced disease and the cure rate with earlier stages I and II Disease was far less than optimal. Today, with the development of infinitely more sophisticated radiotherapy equipment and the accumulated knowledge of the natural history of Hodgkin's Disease, early stage disease can be cured by this means alone.

However, the development of chemotherapeutic drug regimens has made it possible using chemicals alone to achieve complete remissions (absence of all clinical symptoms) in approximately 75 percent of ALL patients with advanced disease. Even more significantly, over half of these advanced patients are still free of disease five to 10 years after all treatment was ceased and they can thus be considered cured. This 10-year data, developed by the NCI, on what was historically considered one of the most implacable killers of all malignant disease, is an abiding testimony of the merits of the long march of chemotherapy from the dark ages of the 1940's and 1950's.

(more)

HODGKIN'S DISEASE (CONT'D)

Even more important is the fact that development of effective treatment using both local radiotherapy and systemic MOPP, has given clinical investigators the tools necessary to complete, in the 1970's, those experiments necessary to develop even more effective and less toxic treatments of Hodgkin's Disease. And the lessons learned in continuing this long march probably will result in more effective and less disfiguring treatments for many other cancers, Dr. DeVita said.

#

NEW METHODS DEVISED TO STUDY LYMPHOMAS

Recent advances in immunology may help physicians categorize cancers of the lymph system more accurately, according to Dr. Costan W. Berard and co-workers at NIH's National Cancer Institute.

Dr. Berard discussed new methods for studying the lymphomas at a meeting on September 30, 1977, of the National Conference on the Lymphomas and the Leukemias in New York City. The meeting was cosponsored by the National Cancer Institute and the American Cancer Society.

Lymphoma is a term for several types of cancer of the lymph system. Among these are lymphoblastic lymphoma, in which the malignant cell is a lymphoblast, a white blood cell (lymphocyte) in the early stages of development; lymphocytic lymphoma, in which the major cell type is the mature lymphocyte; and follicular (nodular) lymphoma, a cancer of the lymph node in which the node is distorted and enlarged by the growth of follicles within it. The lymph system comprises the lymph nodes and related organs, the white blood cells (lymphocytes) manufactured by the lymph tissue, and the lymph fluid within the vessles. Lymphocytes are active in the body's immune defense against disease.

The lymphomas are classified by the appearance of cells and lymph nodes under the microscope. Recent advances in immunology have led scientists to reexamine the traditional classifications of the lymphomas. New methodologies have established the lymphomas as cancers of the immune system.

Several types of lymphocytes (white blood cells) are included in the immune system. Two of the most important are the B-lymphocytes and the T-lymphocytes. These cells play different roles in the immune system yet they cannot be distinguished one from the other under a microscope. The cells can be

(more)

LYMPHOMAS (CONT'D)

identified, however, by characterisitc markers on the surface membrane.

Scientists have been comparing the immunologic reactions of cells from lymphoma patients with those of cells from disease-free persons. They have found not only that the lymphomas are cancers of the immune system, but also which of the two major types of lymphocytes is associated with a specific lymphoma. For example, subpopulations of B-lymphocytes have been found to be responsible for Burkitt's lymphoma, follicular (nodular) lymphomas, and certain lymphocytic lymphomas. T-lymphocytes have been associated with lymphoblastic lymphomas, mycosis fungoides, and Sezary's syndrome.

Scientists have not yet determined the precise nature of the abnormal cells of Hodgkin's disease, a cancer marked by the progressive enlargement of lymph nodes, spleen and other lymphoid tissue throughout the body. The Reed-Sternberg cells that are characteristic of Hodgkin's disease may be derived from histiocytes, another kind of white blood cell.

"These immunologic methods do not replace the microscopic diagnosis of cancer," said Dr. Berard, "because at present they cannot *per se* tell whether the cell is normal or cancerous. But we've learned a great deal about the origin and growth of these cells. We hope that in the future this knowledge will be a valuable diagnostic tool and an aid to cancer therapy."

#

PERITONEOSCOPE CAN BE USED TO BIOPSY THE LIVER

Surgery may not be necessary to determine the extent of disease in the majority of patients with non-Hodgkin's lymphomas, according to Dr. Bruce A. Chabner of NIH's National Cancer Institute, (NCI).

Staging laparotomy, an operation in which the spleen and abdominal lymph nodes are removed and multiple biopsy samples are taken of the liver, has often been used to determine the spread of non-Hodgkin's lymphoma in a patient's abdominal cavity. Instead, Dr. Chabner and coworkers found that the same type of information could be obtained with a non-operative procedure in which an instrument called a peritoneoscope is used to biopsy the liver and explore the abdomen.

The NCI physician discussed these findings on September 30, 1977, at the National Conference on the Lymphomas and the Leukemias in New York City. The meeting was cosponsored by the National Cancer Institute and the American Cancer Society.

The non-Hodgkin's lymphomas are a group of cancers that develop in the lymph glands and other body organs that produce white blood cells. Staging, a diagnostic process that determines the extent of spread of the lymphoma, is required to plan appropriate therapy. Patients with localized non-Hodgkin's lymphomas (Stages I or II) can be treated effectively with radiation therapy to the lymph nodes, whereas patients with widespread disease (Stages III or IV) require chemotherapy or total body irradiation. Unless the staging procedures are rigorous, disseminated disease can be easily missed, Dr. Chabner said.

Beginning in 1971, a staging study was done on patients admitted to the NCI for treatment of non-Hodgkin's lymphomas. A total of 170 patients took

(more)

part in the study. Eighty-one of these patients had a nodular form of non-Hodgkin's lymphoma; 89 patients had a diffuse form. The terms "nodular" and "diffuse" describe the pathology of the lymph node. In nodular lymphoma the cancerous cells tend to cluster together forming discrete follicles, whereas in diffuse lymphoma the cancerous cells are widely and uniformly distributed throughout the lymph node.

When referred to the Institute, 58 of the 170 patients (34 percent) were thought to have localized disease. Clinical staging was done in a sequential manner and included physical examination, blood tests, chest X-ray, lymphangiography (X-ray of the lymph system), bone X-rays and scans, and bone marrow biopsies. These diagnostic procedures, preceding examination of the abdomen, revealed that 126 (76 percent) of the patients had advanced stages of non-Hodgkin's lymphoma, Dr. Chabner reported.

Presence of disease in the liver was first assessed by needle (percutaneous) biopsy. This procedure is usually not sufficient to determine the extent of spread accurately, Dr. Chabner said. Ninety-one of the 105 patients with negative liver biopsies had peritoneoscopy, a procedure in which a lighted, flexible tube is inserted through a small incision into the abdomen. Organs within the abdominal cavity can be viewed through the tube, and multiple samples taken of the liver. Twenty-six patients (29 percent) had positive findings not detected by needle biopsy.

At the conclusion of non-surgical liver biopsies, 141 of the 170 patients (83 percent) were found to have Stage III or IV disease. Liver biopsies were positive more often in those patients with nodular pathology.

(more)

PERITONEOSCOPE (CONT'D)

Laparotomy was performed on 44 of the 75 patients who remained in Stages I, II or III. Whereas 11 of the patients were found to have additional sites of Stage IV disease, only 3 patients shifted from a localized to an advanced stage after surgery, a finding that influenced the type of treatment. Dr. Chabner reported that about 25 percent of patients who undergo staging laparotomy have significant postoperative problems including pneumonia, gastrointestinal bleeding, pancreatitis (infection of the pancreas) and pulmonary embolism (blood clots in the lung). These problems do not occur after peritoneoscopy.

Patients with nodular lymphomas nearly always have advanced disease, Dr. Chabner said. This accounted for 94 percent of the 81 patients in the NCI study. These patients can be staged with limited procedures such as physical examination, percutaneous or peritoneoscopy liver biopsy and bone marrow biopsy. Patients with diffuse lymphoma, on the other hand, require extensive staging to distinguish between local and widespread disease. In these patients peritoneoscopy should be performed before resorting to laparotomy, he recommended.

#

GRANULOCYTES MAY HELP CERTAIN LEUKEMIA PATIENTS

Transfusions of granulocytes may increase the probability that leukemia patients with low white blood cell counts will survive a serious bacterial infection. Dr. Arthur S. Levine, Chief of NIH's National Cancer Institute Pediatric Oncology Branch, discussed this finding on September 29, 1977, at the ACS-NCI National Conference on the Leukemias and the Lymphomas in New York City. The meeting was sponsored by the National Cancer Institute and the American Cancer Society.

Granulocytes are a class of white blood cells that are important in fighting infection. Patients with leukemia become depleted of granulocytes (granulocytopenic) by their disease and by the drugs used to treat the disease. This condition sets the stage for life-threatening infections, such as septicemia (bacterial infections of the blood stream). Whereas antibiotics have been useful in treating septic cancer patients, they may be less effective when the patient has prolonged granulocytopenia, Dr. Levine said.

A study to determine whether cancer patients might benefit from granulocyte transfusions was begun at the National Cancer Institute in 1973. Twenty-seven granulocytopenic patients with documented septicemia were randomized to receive either antibiotics alone or antibiotics plus daily transfusions of granulocytes from immunologically compatible donors. Transfusions were continued until the patient's own granulocyte count was once again normal or until all signs of infection were gone.

Five of the 14 patients who received only antibiotics survived the bout of bacterial infection, whereas 12 of the 16 transfused patients survived, Dr. Levine said.

A striking finding was that survival of infected patients who did not

(more)

GRANULOCYTES (CONT'D)

receive transfusions depended upon the patient's ability to recover a normal granulocyte count rapidly. None of the eight patients who received antibiotics alone and who did not recover a normal granulocyte count within one to two weeks survived. However, eight of the 12 transfused patients survived their infection despite persistent granulocytopenia, Dr. Levine said. Transfused and untransfused patients with rapid white blood cell recovery faired equally well.

Despite the success of white blood cell transfusions in controlling infections in this group of patients with advanced cancer, the transfusions did not substantially increase their survival in the long run. All died of their cancer. The study does suggest avenues for further research, Dr. Levine said. Perhaps transfusions might be of value in preventing infection in newly diagnosed patients with granulocytopenia. Recently diagnosed acute myelogenous leukemia patients, for example, may remain granulocytopenic for prolonged periods while attempts are being made to induce remission with drugs. Several clinical studies are underway to examine the role of prophylactic transfusions in this group of patients.

The NCI physician also discussed improvements in techniques for collecting granulocytes from donors. Two current methods employ either a continuous-flow centrifuge to separate the granulocytes on the basis of their sedimentation characteristics, or a column in which granulocytes selectively adhere to a nylon wool filter.

The continuous-flow centrifuge is an expensive instrument and is limited in the number of cells that can be harvested from a single donor. A new rotor,

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GRANULOCYTES (CONT'D)

developed at the Oak Ridge National Laboratory, can increase substantially the number of granulocytes obtained with the continuous-flow centrifuge, Dr. Levine reported.

The filter process yields a large number of cells, but they are often damaged in the collection process. Patients who receive cells collected by this method may experience side-effects, such as chills and fevers. Preliminary studies at the National Cancer Institute suggest that administration to donors of a single dose of colchicine, a drug used to treat gout, may lessen the damage to white blood cells harvested by the filtration method.

The role of granulocyte transfusions in cancer patients requires more research, Dr. Levine said. He added that the results of the NCI clinical study, as well as studies at other U.S. institutions, are just beginning to define that role.

#

February 1978

DOCTORS SEEK GONORRHEA DRUGS OTHER THAN PENICILLIN

Penicillin is no longer the clearcut drug of choice for the treatment of gonorrhea. For many years, increasingly large doses have been required for effective treatment, and within the past year, totally resistant, penicillinase-producing strains of *Neisseria gonorrhoeae* have emerged in this country. For these and other reasons, investigators are looking for alternative methods of gonorrhea treatment.

A recent report by investigators, whose work is funded by NIH's National Institute of Allergy and Infectious Diseases, that both spectinomycin and tetracycline are equally acceptable alternatives to penicillin for the treatment of gonorrhea, although each has distinct advantages and disadvantages.

During a two-year period, 4,063 patients were treated randomly with either a single dose of two or four grams of spectinomycin or a four-day regimen of nine grams of tetracycline. Both drugs were quite effective for initial therapy of gonorrhea. With either drug, the cure rate for anogenital infection was a minimum of 94 percent for both men and women, and the failures included possible reinfections.

One of the purposes of this study was to determine whether extensive use of these antibiotics would lead to the development of drug-resistant strains. Although in this study recurrence of infection after spectinomycin treatment was not due to resistant organisms, it is likely that widespread use of this antibiotic eventually would lead to spectinomycin-resistant gonococci. Scattered reports of such strains have already appeared in the literature.

The prevalence of tetracycline-resistant organisms increased during the study indicating that widespread use of tetracycline for initial therapy would

GONORRHEA DRUGS (CONT'D)

rapidly result in selection of drug-resistant strains. The problem is accelerated by patients who do not complete the full four-day regimen.

The investigators concluded that gonococci are capable of developing resistance to penicillin, spectinomycin, and tetracycline, and that no one drug is entirely satisfactory. Spectinomycin, rather than tetracycline, is indicated for penicillin-resistant and penicillinase-producing strains of gonococci. However, spectinomycin does not eradicate *Chlamydia trachomatis*, another sexually transmitted pathogen which causes many cases of non-gonococcal urethritis and is present in 20 to 60 percent of patients with gonorrhea. They emphasized the importance of careful follow-up to be sure that treatment, by whichever drug, has been successful.

This study was reported by Drs. Walter W. Karney, Alf H. B. Pedersen, Morton Nelson, Harry Adams, Robert T. Pfeifer, and King K. Holmes from the University of Washington School of Medicine, and U.S.P.H.S. Hospital in Seattle, the Seattle-King County and Alameda County Health Care Services Agency, Oakland, California, and the University of California College of Medicine. It appeared in *The New England Journal of Medicine*.

#

NICHD STUDIES SOME SUBSTANCES THAT MAY CAUSE BIRTH DEFECTS

A recently discovered genetic system, enabling the body to be protected from drug and other foreign substance poisoning, may render some individuals susceptible to birth defects. This is a finding of NIH's National Institute of Child Health and Human Development scientists working with Dr. Daniel Nebert, chief of the Developmental Pharmacology Branch.

According to Drs. Nebert, Shu Shum, and George Lambert, offspring of pregnant mice treated with poisonous chemicals called polycyclic hydrocarbons differ in their ability to metabolize them.

Fetuses converting the toxicants into a different form are far more likely to be deformed, stunted, or killed than fetuses metabolizing the chemicals less efficiently.

In the strains of mice studies, the individual mouse's capacity to metabolize hydrocarbons is determined by a genetic system, and "*a*romatic *h*ydrocarbon responsiveness locus."

The *Ah* locus, discovered by Dr. Nebert and his co-workers more than six years ago, is present in many animal cells, including man. It consists of one gene or a small number of genes which control the body's capacity to rid itself of numerous toxic substances.

Among these are hydrocarbons in cigarette smoke, charocoal-broiled foods, and automobile exhaust fumes. Other chemicals whose fate is determined by the *Ah* locus include fat-soluble compounds used as drugs, insecticides, and raw materials for industry.

If allowed to accumulate in the tissues, many of these substances are poisonous and may cause cancer, mutations, or birth defects. When one of the

(more)

toxicants enters a cell, the *Ah* locus in the cell's nucleus is activated in some as yet unknown manner.

Activation of the *Ah* locus boosts the activity of a series of enzymes called monooxygenases. These enzymes modify the original toxic chemical into a new substance which can be attacked and further degraded by another set of enzymes called conjugating enzymes. The final product will be a harmless substance which can be excreted from the cell and from the body.

Individual humans and various strains of laboratory mice differ in their enzymatic response to hydrocarbons. In mice having a "responsive" form of the gene(s) at the *Ah* locus, hydrocargon exposure brings about a dramatic rise in monooxygenase enzyme activity.

In other mice, called "nonresponsive," the increase does not occur at all in the liver and is small in all tissues other than liver. When a responsive mouse is mated with a nonresponsive mouse, the offspring are usually responsive. Genetically, it can be said that aromatic hydrocarbon responsiveness in mice, like brown eye color in humans, is inherited as an autosomal dominant trait.

Through a series of crosses between genetically responsive and genetically nonresponsive mice, Drs. Shum and Nebert studied preganancies in which fetuses of both genetic types were present in the same womb. In this situation, early exposure of the pregnant mouse to a polycyclic hydrocarbon causes massive damage to fetuses with the responsive gene(s) at the *Ah* locus.

About 75 percent of these fetuses are deformed or killed, and virtually all the survivors are growth retarded. In contrast, their nonresponsive littermates suffer fewer malformations, only a slight growth inhibition, and a much lower

(more)

death rate.

Malformations observed in this study include cleft palate, club foot, absence of an eye, nose and jaw underdevelopment, kidney or liver abnormalities, and heart protrusion outside of the body cavity.

This study proves that genetic factors within fetal tissues can determine fetal susceptibility to birth defects when the baby in the womb is exposed to chemicals by way of the mother.

Results also suggest a possible explanation for the low birth weight of human infants whose mothers smoked cigarettes during pregnancy. It seems likely that this form of intrauterine growth retardation may be caused by hydrocarbons "triggering" the *Ah* locus.

For an adult animal receiving hydrocarbons in its food, having the responsive form of the gene(s) at the *Ah* locus can be of considerable survival value. This trait enables the animal to dispose of the hydrocarbons more efficiently. However, for the embryo or fetus exposed to hydrocarbons at a critical point in its development, the responsive form of the gene is a liability.

This apparent contradiction can be explained partially by earlier studies showing that the first products of monooxygenase activity are highly reactive compounds. They can damage the cell's genetic material if not detoxified immediately.

Apparently, fetuses genetically responsive to hydrocarbons may form these dangerous intermediates in sufficient quantity to cause irreparable damage to their tissues. The nonresponsive fetuses seem to be protected by their inefficiency in coping with hydrocarbons.

Another possible explanation for vulnerability of the responsive fetuses

(more)

is that these monooxygenases are capable of metabolizing hormones normally in the body as well as foreign chemicals. When monooxygenase activities are prematurely "triggered" by a foreign hydrocarbon, the fetus may break down hormones needed for normal growth and development.

This mechanism could explain the high incidence of low birth weight observed in the responsive fetuses.

Laboratories around the world are now attempting to apply *Ah* locus information to the prevention of human disease. A search is underway to identify human groups or individuals whose *Ah* responsiveness places them at risk for diseases caused by environmental chemicals.

NICHD researchers are collaborating with NIH's National Eye Institute investigators to determine whether the *Ah* locus plays a role in causing cataracts to form in response to certain drugs and in causing retinitis pigmentosa, a degenerative disease of the eye.

Current NICHD studies aim at a more detailed understanding of the monooxygenase enzymes and the genetic control mechanisms enabling the *Ah* locus to respond to hydrocarbons.

In the exploratory phase, the group's work has already begun illuminating one of the most mysterious areas of human biology--the area of gene-environment interaction. From their work and other scientists' work, it may someday be possible to detail how a specific gene and a specific environmental pollutant act together at the cellular level causing death, disease, and disability.

#

NIEHS WILL HELP PROVIDE MORE TOXICOLOGY MANPOWER

NIH's National Institute of Environmental Health Sciences (NIEHS) in Research Triangle Park, North Carolina is sponsoring two new programs to respond to the Nation's needs for additional scientific expertise in toxicology and related fields.

The two programs will help provide the manpower necessary to meet the mandates set forth in the Toxic Substances Control Act of 1976. The Act calls for the identification, scientific evaluation, and testing of substances, not normally found in nature, that are suspected of possessing toxic properties.

Training programs will be sponsored at research institutions across the country, supporting training for toxicologists, environmental pathologists, and epidemiologists. When trained, these new scientists will be able to identify potential environmental hazards, make judgements concerning their effect on human health, and make this information readily available to the general public, legislators, industry, and Federal agencies charged with the control or regulation of substances found to be deleterious to human health and well-being. This program is the major Federal manpower development effort in response to the Toxic Substances Control Act.

The NIEHS is also launching the Academic Investigator Award--Toxicology (AIA-T) program that is designed to stimulate individuals with research expertise in biomedical science toward careers in environmental toxicology. Scientists trained in other disciplines will be afforded up to three years training under the guidance of a sponsor who is established in the field of environmental toxicology. This training will be conducted at institutions where the academic environment is conducive to rapid orientation of the investigator to the scientific

(more)

MANPOWER (CONT'D)

and regulatory facets of human environmental health problems. The product of this program will be scientists well-founded in their disciplines with knowledge about research techniques and problems in environmental toxicology.

#

MAYO CLINIC INVESTIGATORS DESIGN NEW X-RAY MACHINE

In early September, engineers in Wayland, Massachusetts, began constructing a new, revolutionary diagnostic X-ray machine that will allow doctors to view the heart, lungs, and circulation in three-dimensional motion. The machine was developed during a five-year period by a team of multi-disciplined researchers at Mayo Clinic, Rochester, Minnesota, and contracted out to Wayland's Raytheon Corporation for construction.

The new X-ray scanning device, called a "dynamic spatial reconstructor" or DSR, was designed with the help of a sophisticated computer system funded for Mayo by the Biotechnology Resources Program of NIH's Division of Research Resources. NIH's National Heart, Lung, and Blood Institute is providing $3.1 million for construction of the machine.

The Mayo team which developed the DSR is headed up by Dr. Earl Wood, a pioneer in the study of heart and circulatory physiology. According to Dr. Wood, the diagnostic capabilities of the DSR will include:

--Information on the extent of muscle damage after a heart attack

--Diagnosis of complex congenital heart defects

--Detection of coronary artery disease, including narrowing or clogging of the arteries and the resultant changes in blood supply to the heart muscle

--Detection of potentially fatal aneurysms, weaknesses in the blood vessels leading from the heart that usually can be repaired if detected early

--Easier and more reliable identification of lung and other tumors which affect anatomy or blood flow within an organ

According to the developers, the DSR will go well beyond the current generation of X-ray scanning devices which produce only static images of internal organs. Dr. Wood says the DSR should be better for diagnosing heart, lung, and

(more)

X-RAY MACHINE (CONT'D)

circulatory diseases because it will operate at a higher speed and, hence, show body organs in motion. Also, because it will provide a truly three-dimensional view, mathematical slicing of the organ in any direction for detailed studies of its internal structure will be possible.

The design for the machine calls for 28 X-ray tubes positioned around 180 degrees in a circular structure which will rotate around the patient. The X-ray tubes can be turned on and off in very rapid sequence so that 28 angles of view can be obtained in one hundredth of a second as often as 60 times per second. These X-ray views then will be converted into an electronic form and stored on a video disc similar to those used for sports instant replays on television.

Using the Division of Research Resources funded computers, the Mayo investigators then are able to convert the 28 multiplanar conventional X-ray views stored on the video disc to numerical form. This information is then reconstructed by the computer into sets of up to 250 cross-sectional images encompassing the entire extent of, for example, the heart so that complete pictures of its surfaces and internal structures can be obtained as often as sixty times per second as it is beating within the chest.

"What happens," Dr. Wood explains, "is the computer allows us to take 28 standard X-rays and convert them to new types of images which allow us to look at any view of the inside of the body which could be helpful in determining the nature, location and extent of a given disease problem."

In effect, the body can be thinly sliced mathematically in any direction so that its internal structure can be studied in detail. The conversion from

(more)

standard X-rays to multiple slices is carried out when the standard views are put into numerical form by the computer and then reconstructed from these numerical values by the computer into the particular sectional views which the physician may indicate he wishes to examine.

When the diagnostician wants to look at any single or multiple sections of the body that was X-rayed by the DSR, the stored digital numbers will be converted into the desired sectional video images. These computer-generated pictures will be displayed on a television screen in the same views as the physician would use if the tissue in question had actually been removed from the body and sliced open so as to study its internal structure.

The process will be more convenient for individual patients than those now employed by current scanners because machines now in use take several minutes to obtain a few cross-sectional views of a part of the body while the DSR will obtain views of many sections in less than a second. Also, the short scanning time will allow study of greater numbers of individuals and, hence, help to reduce the cost per patient.

The DSR is not expected to be in conventional use until the early 1980s, following additional testing at Mayo once the machine is built. The construction of the original unit is expected to take approximately 18 months.

(more)

X-RAY MACHINE (CONT'D)

Dr. Earl Wood of the Mayo Clinic explains a video image which is the final product of the Dynamic Spatial Reconstructor, a new X-ray unit developed by Dr. Wood and his colleagues. The video images, which show three-dimensional views of the body, are produced with the help of a sophisticated computer system funded for Mayo by NIH's Division of Research Resources. (N I H Photo # 1606)

#

NIGMS MAKES UNDERGRADUATE TRAINING GRANT AWARDS

Twelve undergraduate schools have been awarded first-year grants, totaling almost $1 million, from the National Institutes of Health to increase opportunities for minority students to achieve careers in the health sciences.

The grants will aid in developing new training programs in the biomedical sciences for outstanding students who wish to prepare for graduate studies in biomedical research and teaching.

Students chosen by the schools to enter programs will be given funds to pay tuition costs and living expenses.

This grants program is the first at NIH to give direct support for research training at the pre-baccalaureate level.

The honors undergraduate training grant awards program was recently initiated by the Minority Access to Research Careers (MARC) Program of the National Institute of General Medical Sciences, a component of the NIH.

Congress, in addition, has taken special cognizance of the MARC Honors Undergraduate Award effort by appropriating specific funds for the fiscal year 1977.

Institutions eligible for the awards are the Nation's four-year undergraduate colleges and universities in which student enrollments are drawn substantially from ethnic minority groups known to be under-represented in the health sciences.

These minorities currently include American Indians, Blacks, Hawaiians, Mexican Americans and Puerto Ricans.

The first of the undergraduate awards were made last Fall, after review of applications from 64 schools. Review for scientific merit was performed by a committee of peers from the academic community.

(more)

TRAINING GRANTS (CONT'D)

Financial support for the recipient schools is expected to continue annually, for at least five years.

In general, the individual school training programs will accomodate up to 10 students per year, with trainees chosen to enter in their junior year on the basis of academic performance and scientific interests.

Special curricula, encompassing advanced courses in biology, chemistry, physics and psychology, will be further enriched by field trips, scientific seminars and student participation in laboratory investigations. Individual students will be given an opportunity to spend time at a major institution where nationally recognized research in the student's field is being performed.

In this way, a greater number of minority students will be prepared to compete successfully for entry into graduate programs leading to the doctorate degree and productive careers in biomedical research.

#

NIDR PUBLISHES BOOK ON SWEET PREFERENCE

In the search for ways to combat the Nation's sweet tooth and thereby improve dental and general health, NIH's National Institute of Dental Research has just published *Taste and Development: The Genesis of Sweet Preference.* The book contains the proceedings of a symposium sponsored by the NIDR and NIH's Fogarty International Center.

The NIDR is encouraging the study of the development of taste--from the fetus, to the newborn, toddler, child, teenager, and adult--to find out how detrimental eating habits develop. From this approach ways to prevent or to change such patterns should emerge.

Tooth decay, which affects nearly all Americnas, can be controlled by diet. The overeating of sweets also contributes to obesity, diabetes, and heart problems. Conventional motivational techniques have failed to persuade people to limit sweets. Therefore, new techniques must be developed through basic nutritional and behavioral study.

The symposium, which was held at the NIH campus in Bethesda, in June 1974, and the new book bring together advances from taste research conducted on adult subjects with recent studies on animal fetuses and human newborns that have required development of new methodology. For example, the book contains reports that the sense of taste appears to function before birth in some species and that the taste receptors already are developed in the fetus. Physiological studies demonstrate the lamb sucking and swallowing before birth. Furthermore, newborns--be they human, pig, rat, or hamster--respond positively to sweet taste by drinking more of solutions with a sweeter taste.

Learned associations with sweets have an influence on food selection

(more)

SWEET PREFERENCE (CONT'D)

throughout life. Young rats learn from older ones to choose certain foods and to avoid poisoned ones, according to reports made at the symposium. Children in most cultures receive sweets as rewards and at joyous occasions. Thus, the preference for sweets, which is present at birth, may be further increased by experience.

A limited number of single copies of the hard-bound publication can be obtained from its editor Dr. James M. Weiffenbach, Oral Pharyngeal Development Section, National Institute of Dental Research, Building 31, Room 3B-10, National Institutes of Health, Bethesda, MD 20014. The book is available for $9.00 from the Superintendent of Documents, U.S. Government Printing Office, Washington, DC 20402. When ordering from the GPO, include a check or money order and request by title and stock number 017-047-00009-4, DHEW Publication No. (NIH) 77-1068.

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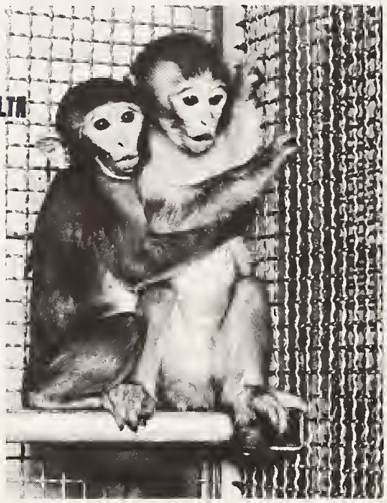

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March 1978

NEWS & FEATURES From NIH

NIAID DESCRIBES IMMUNOLOGIC AND BIOCHEMICAL INTERACTIONS THAT PRECIPITATE ASTHMA ATTACK

The sequence of immunologic and biochemical interactions precipitating an asthmatic attack, and approaches toward interference with the process were described on December 13, 1977, at a NIH Science Writers Seminar in Bethesda.

Dr. Michael A. Kaliner, of NIH's National Institute of Allergy and Infectious Diseases, described the many chemical mediators known to be released during an asthmatic attack by mast cells located primarily in the peribronchial region of the lung. Mast cells are ordinarily coated with IgE antibodies. In persons with allergic disease such as asthma, these IgE antibodies are directed against usually harmless airborne or ingested particles such as pollen grains and dust. When mast cells encounter these particles, a dramatic expulsion of granular materials occurs.

Best known among the chemicals released from the granules is histamine. Other chemicals released are the slow-reacting substance of anaphylaxis (SRS-A), eosinophil chemotactic factor of anaphylaxis (ECF-A), prostaglandin E and prostaglandin F_{2a}, superoxide radical (an unstable form of oxygen), the enzyme superoxide dismutase, platelet-activating factor(PAF), and probably a host of other compounds.

The above compounds are known to be mediators of anaphylaxis (allergic shock). Their effects on target tissues account for many abnormalities found in patients with asthma: smooth muscle constriction, fluid retention causing swelling of mucosal tissues that line the airways, attraction of eosinophilic white blood cells to the area, excessive secretion of mucus, parasympathetic efferent discharges that may result in further muscle constriction and mucus secretion, shedding of epithelial cells that line the lung, and aggregations

(more)

of blood components (platelets) important in blood clotting.

Some drugs useful in treating asthma block the release of these mediators. Beta-adrenergic agents such as isoproterenol increase the levels of cyclic AMP, a ring-shaped molecule through which some hormones act, and thereby prevent release of these allergy-associated mediators.

Other drugs such as aminophylline (a methylxanthine) inhibit the breakdown of cyclic AMP and also suppress mediator release. Combinations of beta-adrenergic agents plus methylxanthine are extremely effective in preventing and treating asthmatic attacks.

Dr. Kaliner noted that, conversely, acetylcholine (neurohormone released by parasympathetic nerves) increases the release of mediators and also increases cyclic GMP (a companion chemical and sometimes antagonist of cyclic AMP). His experiments providing evidence for this were described in the September 1977 *Journal of Allergy and Clinical Immunology*. In that report he also observed that in addition to acetylcholine, other potentially important compounds such as histamine, serotonin, and prostaglandin F_{2a} also raise cyclic GMP levels and may possibly initiate a self-perpetuating cycle of toxic mediator release.

More recently, in the October 1977 *Journal of Clinical Investigation*, he reported that the presence of microorganelles called microtubules within the mast cells are essential for mast cell degranulation. Dr. Kaliner also found that the enhancing and suppressing activities of cyclic GMP and cyclic AMP, respectively, on secretion of histamine and SRS-A occur through changes in microtubular structure.

Dr. Kalinar said that a means to utilize this information clinically is an objective of his research efforts.

#

NEW DATA ON HOW ANTIBODIES ACT DURING ALLERGIC REACTIONS

Recent evidence on how antibodies (immunoglobulins) act during allergic reactions, whether minor or severe, was described at an NIH Science Writers Seminar in Bethesda on December 13, 1977.

Dr. Henry Metzger of the NIH's National Institute of Arthritis, Metabolism, and Digestive Diseases, described research in his laboratory demonstrating that an aggregation of at least two antibodies of the IgE class are needed on a cell surface before the troublesome, allergy-related chemical called histamine is released. The aggregation of the antibody, in turn, leads to aggregation of at least two receptor proteins on the cell surface to which the IgE antibodies can bind.

Dr. Metzger and associates used rat mast cells, known to be a source of histamine, in several earlier experiments. Mast cell-like cancer cells which can be grown in culture were also used. (Blood cells called basophils also contain and release histamine, and have been utilized in studies at other laboratories.)

In NIH studies reported in 1976, Dr. Metzger's group used IgE labeled with visible dyes (e.g., fluorescein) in order to show that receptor molecules on the mast cell surface each bind only a single molecule of IgE. In the current work, isolated crosslinked pairs of IgE molecules were shown to bind to mast cell surfaces, and in tissue culture they released histamine or serotonin. The antibody pairs, called dimers, also bound to mast cell surfaces in live rats and caused allergic shock in the skin.

NIH scientists Dr. David M. Segal of the National Cancer Institute and Drs. Joel D. Taurog and Metzger of the National Institute of Arthritis, Metab-

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ANTIBODIES (CONT'D)

olism, and Digestive Diseases concluded *(Proc. Natl. Acad. Sci., July 1977)* that IgE crosslinked to form dimers serves as the minimal essential signal to trigger IgE-mediated secretion from mast cells.

In summarizing some earlier research of importance in this field, Dr. Metzger noted that in 1966 Drs. Kimishige and Teruko Ishizaka, formerly at the National Jewish Hospital and Research Center in Denver, were the first to demonstrate that IgE is the predominant antibody involved in allergic reactions.

Part of the groundwork for their finding, he noted, was laid in the 1950s by Dr. Eliot Middleton at Columbia University College of Physicians and Surgeons in New York City. Dr. Middleton found that a normal person's white blood cells, when exposed to cell-free blood from an allergic individual, were transformed into allergic cells that released histamine when confronted with an offending allergen. This facilitated the search for and discovery of the non-cellular circulating antibody, IgE.

IgE is made and secreted by plasma cells, which are mature white blood cells derived from the B-cell type of lymphocytes. Once secreted, the IgE antibody circulates and when encountering and attaching itself to a basophil or mast cell, binds to the cell surface receptor via a specialized portion (Fc end) of the antibody structure.

Dr. Metzger described the cell with IgE on its surface as analogous to a naval mine, "perfectly harmless until an allergen or other antigen capable of binding to the IgE comes into contact with it. When this happens," he said, "an explosive release of histamine and other substances potent in blood vessel chemistry takes place."

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ANTIBODIES (CONT'D)

Dr. Metzger and his colleagues are trying now to characterize the IgE-binding receptor proteins on the surface of mast cells and basophils, and to define the receptor's role in the release of histamine.

Dr. Metzger said that he, like others working in this research field, consider that an understanding of these events may improve understanding of other antibody-associated events in various disease states and in good health, as well as improving the chances to find specific drugs to combat allergies.

#

NIAID STUDIES BODY CHEMISTRY OF PATIENTS WITH HIVES, ANGIOEDEMA

A scientist of NIH's National Institute of Allergy and Infectious Diseases described the intricate body chemistry now being deciphered while studying patients with hives and angioedema (swelling related to the action of chemicals upon blood vessles, especially those in the skin).

Dr. Allen P. Kaplan, speaking at a NIH Science Writers Seminar in Bethesda on December 13, 1977, provided new information on these irritating, occasionally fatal diseases that consistently create problems for about two million persons in the U.S. His talk was based in part on a scientific report he presented in the November 1977 *Journal of Allergy and Clinical Immunology*.

Dr. Kaplan said that hives are formed following the leakage of one or more permeability factors, especially histamine, from dilated blood vessels in the upper layer of the skin's dermis. When a similar process occurs at deeper layer of the skin or subcutaneous tissues, angioedema or swelling results.

Both allergic and non-allergic reactions can cause the formation of hives and angioedema. The mechanisms of release of histamine, other permeability factors, and of blood vessel dilators such as kinins, vary depending upon the particular disorder.

At the NIH Clinical Center, Dr. Kaplan has most recently studied hives that are physically induced--triggered by cold, heat, pressure and exercise--because they can be induced safely in a reproducible fashion in clinical surroundings. For instance, when an ice cube is placed against the arm of a patient with cold urticaria for five minutes, large amounts of histamine are found in blood samples drawn from an arm vein during the ensuing 15 minutes, during which time itching and swelling occur. A drop in blood pressure is also

(more)

noted if the patient is further exposed to ice water. Upon removal of the cold stimulus, the symptoms slowly abate.

Under non-laboratory conditions, Dr. Kaplan noted that patients with cold urticaria have died while swimming in cold water because of sudden, massive release of histamine followed by sharply lowered blood pressure; they faint and drown.

In some patients with cold urticaria, circulating IgE antibody has been shown to be capable of transferring the cold sensitivity to normal skin. However, scientists do not know the mechanism by which a temperature change, instead of the usual antigen-antibody reaction, causes the histamine release. Use of the antihistamine cyproheptadine (Periactin$^{(R)}$) has been reported by A.A. Wanderer and E.F. Ellis (*J. Allergy Clin. Immunology, 1971*) to markedly diminish these cold-dependent reactions.

In another type of hives called cholinergic (neurochemically-stimulated) urticaria, the hives may be induced by hot showers, exercise, or acute anxiety. Neither antibodies nor allergic reactions appear to be involved. However, the patients have an abnormal sensitivity to the neurotransmitter acetylcholine which is released by certain nerves and stimulates muscles and sweat glands. Hives are a consequence, and elevated histamine levels have been observed in the blood plasma of some patients during severe episodes.

Patients with chronic hives of unknown origin have normal histamine levels in their blood plasma. However, in studies following use of a new technique that creates small suction blisters on the skin, skin histamine levels among patients with chronic hives were shown to be clearly elevated in contrast to

(more)

lower histamine content of suction-induced blisters among normal volunteers.

Kinins, chemicals that dilate blood vessels and are derived from plasma proteins, apparently play a key role in causing the swelling seen in patients with hereditary angioedema, a potentially fatal disorder. These patients are missing a certain plasma protein: the inhibitor of the activated first component of the blood substance complement, which controls the formation of kinins.

Blood contains nine complement components, C1 through C9. Active C1 digests two complement components, C4 and C2. A fragment derived from C2 appears to be further digested to yield a kinin. The activated C1 inhibitor, not surprisingly, inhibits activated C1 and thereby prevents kinin formation. This sequence of events therefore can cause development of angioedema.

The coagulation pathway also forms a kinin called bradykinin (*brady* meaning "slow"). Two clotting proteins, Hageman factor and prekallikrein, activate each other to form activated Hageman factor and the enzyme kallikrein. A high molecular weight form of kininogen is a co-factor and accelerates these reactions. Kallikrein then digests the high molecular weight kininogen to liberate bradykinin. The activated first component of complement also inhibits activated Hageman factor and kallikrein, and thereby prevents bradykinin formation. Thus in the absence of the activated first component of complement, it is possible that the patient's blood plasma tends to form these kinins, and severe episodes of swelling result.

Dr. Kaplan said that recent clinical studies by Dr. Michael Frank and his colleagues at the National Institute of Allergy and Infectious Diseases demon-

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BODY CHEMISTRY (CONT'D)

strated that use of an androgen-like hormone, danazol (Danocrine$^{(R)}$), has induced synthesis of the activated first component of complement while studying patients at the NIH Clinical Center. The synthesis of the inhibitor of the activated first component of complement prevents attacks of hereditary angioedema.

The latter research also demonstrates that hereditary angioedema is not caused by absence of a gene but instead by a hereditary defect in which the gene for normal synthesis of the activated first component of complement is somehow suppressed. The androgen-type hormone stimulates the gene to function.

#

WOMEN ON PILL MAY INCREASE RISK OF TWINS

Women on the Pill may increase their risk of giving birth to twins by conceiving the first month after they discontinue use of oral contraceptives. When pregnancy followed Pill use of at least six months, there were nearly double the number of twins that would have been expected.

Dr. Kenneth J. Rothman, who did this study at the Harvard School of Public Health, says that 25 pairs of twins were born to 1,609 mothers in his study who conceived within one month of terminating Pill use. This rate, 1.6 percent, compares to the usual twinning rate of about one percent.

Twinning increased in relation to length of Pill use, with more twins being born to women who were on the Pill longer. The highest rate of twinning recorded in the study, 2.1 percent, was noted for mothers who conceived within a month of taking the Pill after 13 to 24 months of use. However, Dr. Rothman cautions that this progressive increase could be explained by chance.

More clear-cut was the association between twinning and timing of conception after taking the Pill. In the study of 6,002 pregnancies following oral contraceptive use, 60 resulted in twins, a rate of one percent. This rate jumped to an average 1.6 percent for pregnancies conceived within one month of stopping the Pill. Twins were born at a rate of 1.1 percent for 2,614 mothers who had not used the Pill.

This study, supported in part by NIH's National Institute of Child Health and Human Development, presents the first evidence of increased twinning associated with oral contraceptive use. Such an association had been predicted based on observations of increased levels of hormones thought to control ovulation in women following oral contraceptive use. Previous studies had failed

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PILL (CONT'D)

to confirm an increase in twinning, however.

As part of his research, Dr. Rothman also looked for associations between oral contraceptive use and rate of spontaneous abortion (miscarriage) and birth weight.

He found that rates of miscarriage and stillbirth were slightly smaller for former users of the Pill, a finding consistent with previously published reports. Specifically, he found that among 3,221 pregnancies prior to Pill use, 412 miscarriages and 12 stillbirths were recorded. In 2,126 pregnancies occurring within three years following use of oral contraception, there were 163 miscarriages and three stillbirths.

Dr. Rothman warns that these findings should not be construed to mean that oral contraceptives act to prevent miscarriages or stillbirths. The main significance of these findings, he says, is that they constitute additional evidence that oral contraceptive use prior to conception does not threaten fetal life.

Dr. Rothman could find no association between using the Pill and birth weight.

The Harvard study included women living in the Boston area between the ages of 24 and 50, who responded to mail questionnaires on their oral contraceptive use and child-bearing histories.

Dr. Rothman reported this study in the *New England Journal of Medicine*.

#

WEIGHT GAIN DRUGS NOT SEEN AS CAUSE OF MAJOR BIRTH DEFECTS

Drugs prescribed to limit weight gain during pregnancy may be only moderately useful but they appear to have been absolved of blame as a cause of major birth defects.

These are the conclusions of scientists at the University of California at Berkeley who examined the relationship between the use of appetite-depressant drugs (amphetamines and phenmetrazine) during pregnancy and birth defects. Several previous reports had implicated these drugs as a cause of congenital heart defects and other serious congenital anomalies.

The Berkeley scientists, working under a grant from NIH's National Institute of Child Health and Human Development, compared the pregnancy outcomes of 1,824 women who took prescribed appetite-depressant drugs during different stages of pregnancy with 8,989 women who had not taken such drugs. Both groups included only women who had gestations of at least 37 weeks.

The Berkeley group found that the incidence of severe birth defects was no higher among the children of the women who had taken the appetite-depressant drugs than among the children of women who had not taken such drugs during pregnancy.

The children were examined at birth, at one year, and at five years. At age five, the severe congenital anomaly (SCA) rate was 3.7 percent for the children whose mothers had taken drugs to control weight gain compared to a 3.4 percent rate for the others. This difference was not considered statistically significant. SCA's are defined to include those that are life-threatening or hazardous and that would impair the child's development or well-being if not corrected. Examples include congenital heart disease, cleft lip, or mental

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retardation.

The one exception was the finding of a higher-than-expected number of oral clefts in the offspring of mothers who took amphetamines in the first 56 days of pregnancy following the last menstrual period. Of the 175 children whose mothers were in this category, three children, or one in 58, had oral clefts (two had cleft palate only; one had cleft lip and palate). All three mothers had taken amphetamines during the stage of pregnancy which is the crucial period for oral-facial development.

Of the 10,213 mothers (including those with less than 37 weeks of gestation) in the study who did not take amphetamines during pregnancy, 21 had offspring with oral clefts, an incidence of one in 500. This compares with findings in two large, previously published epidemiological surveys which reported the frequence of oral clefts to be approximately one in 500 to 600.

Because there is no evidence that the use of amphetamines contributed to other birth defects, the authors hesitate to lay the blame for the oral clefts noted in their study solely on amphetamine use. "The clustering of oral clefts could be due to chance, or it is possible that amphetamines act as a factor in the total genetic and environmental causation of oral clefts," they said. (Previously published reports have indicated that multifactorial causation for clefts of the lip and/or palate is probable.)

As a corollary to the study of teratogenicity, the Berkeley scientists also conducted what they termed a "rough" study of the efficacy of appetite-depressant drugs in controlling weight gain during pregnancy. They tested 1,104 women matched for gestational age and weight; half of the group used

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drugs. A comparison of weight gains in four-week periods before and after the prescription showed only short-term and limited reduction of weight gain in the women taking prescribed appetite-depressants.

Women participating in these studies were those reporting for prenatal care between late 1959 and the fall of 1966 at the San Francisco East Bay Area facilities of the Kaiser Health Plan. A broad socioeconomic cross-section was represented, but the current studies were limited to white women.

It should be pointed out that in these studies, amphetamines were used only as prescribed. The authors note that the Food and Drug Administration and the U.S. Congress have recognized the high potential of amphetamines for abuse. The safety of these drugs during pregnancy, especially at dosages higher than prescribed, remains uncertain.

The study was reported in the November 15, 1977, issue of the *American Journal of Obstetrics and Gynecology* by Lucille Milkovich and Bea J. van den Berg, M.D., of the University of California School of Public Health.

#

NONHUMAN PRIMATES
MAY BE "RECYCLED"

A mechanism has been established by NIH's Animal Resources Program for encouraging and assisting in the "re-cycling" of nonhuman primates used as laboratory animals for biomedical research studies.

The Primate Supply Information Clearinghouse, operating under the University of Washington Regional Primate Research Center in Seattle, has been created for this purpose and is now operational. The project is supported by contract with NIH's Division of Research Resources.

With the shortage of primates for laboratory use and the increasing cost of animal procurement, the Animal Resources Program recognized the need to encourage sequential and multiple use of the animals, and to effect direct and speedier communication between users through the newly created Clearinghouse.

Utilizing a computerized data system, the primate supply information will be transmitted to the biomedical research community by the issuance of a weekly *Alerting Bulletin* containing notices of availability of primates, or their tissues and body fluids, and notices of needs.

The overall purpose of the Clearinghouse is to make the best possible use of the available research primates in the country. Investigators and colony managers will be solicited and invited to list their animals available for transfer or to be shared. The Clearinghouse will also publish sources of supply for body fluids and tissues in addition to body organs of sacrificed animals.

It is also anticipated that investigators seeking animals or body fluids and tissues will file their needs with the Clearinghouse. In addition to the weekly *Alerting Bulletin,* the Clearinghouse will conduct a matching service

(more)

PRIMATES (CONT'D)

by computer and will make referrals to possible users. The data base collected may include species used, species bred, probability of animals available for sharing, and availability of social groups for behavioral studies.

"We are promoting and encouraging sequential use of primates," says Manager Maryeva Terry. "Some laboratories may have fully conditioned primates presently not being used because a particular study has been concluded. These animals are maintained sometimes for long periods of time waiting for the next project to come along. They could be used immediately by other investigators thereby making most efficient economical use of these primate animals."

A user survey conducted in 1975 by Mrs. Terry indicated that there was an overwhelming willingness on the part of the primate user community to cooperate on the contemplated service.

There will be no charge for the service which will be available to both government-supported researchers and scientists in private industry using primates in their work.

Efforts will be made to localize this information in order that scientists be aware of potential laboratory animals available in their own area. Particular emphasis will be made in reaching colony managers and managers of research organizations.

The initial mailing of *Alerting Bulletin* will be made to all clients currently on the mailing list of the Primate Information Center, the nationally-known primate information service maintained by the Washington Center for over a decade. In addition, mailings will be made to researchers and organizations on various mailing lists which are of primate research interest.

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PRIMATES (CONT'D)

Scientists using or having need for primates for research purposes may be placed on the list upon request. Write to Primate Supply Information Clearinghouse, Regional Primate Research Center, University of Washington, Seattle, Washington 98105, or call (206) 543-5178.

Laboratory nonhuman primates can be used for simultaneous studies or in sequence, says the Animal Resources Program of NIH's Division of Research Resources. The Primate Supply Information Clearinghouse became operational in January 1978 and will issue weekly bulletins containing notices of availability of primates, or their tissues and body fluids, and notices of needs. The most common primate laboratory animal is the rhesus monkey (the two rhesus pictured above). The diminishing supply and increasing cost of new primate laboratory animals necessitates the "re-cyclying" of animals now in the United States. (NIH Photo #1607)

#

EXPECTANT MOTHERS ADVISED NOT TO SMOKE

Expectant mothers who smoke are jeopardizing their chances of completing a successful pregnancy, according to a recent report from Columbia University School of Public Health epidemiologists.

In a study conducted there, the Columbia scientists found that women who miscarried before the 28th week of pregnancy were almost twice as likely to have smoked during that pregnancy than were women who carried their babies beyond that point.

574 women who aborted spontaneously (miscarried) and 320 women who delivered babies after at least 28 weeks of gestation were interviewed about their pregnancy histories, particularly their smoking habits. Forty-one percent of the women who suffered spontaneous abortions smoked as compared to 28 percent of the women who delivered after a minimum of 28 weeks gestation.

This association between miscarriage and smoking "merits the attention of both women who conceive and wish to retain their pregnancies and of those who provide care" for these women, in the opinion of the Columbia researchers.

This study, conducted by the Columbia University School of Public Health and Columbia University, was supported in-part by NIH's National Institute of Child Health and Human Development (NICHD).

Dr. Eileen G. Hasselmeyer, chief of the NICHD's Pregnancy and Infancy Branch, says that this study strengthens the already strong case against smoking, especially during pregnancy. Previous studies have clearly established that women who smoke while pregnant run a greater risk of having babies with low birthweights. They are also at greater risk for losing their babies through stillbirth or death soon after birth. Low birthweight babies, as a

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rule, have more difficulty getting a good start in life than those of average birthweight.

Exactly what causes this fetal growth retardation in smoking mothers is not known. It may be that the nicotine in smoke causes placental blood vessels to narrow, thereby diminishing the supply of nutrients and oxygen to the unborn child. Or it may be that the abnormal amount of carbon monoxide a smoking mother inhales retards the development of her baby. Some scientists feel that the association can be partly explained by reduced food intake in smokers.

These or other factors may also account for the higher incidence of spontaneous abortion observed among pregnant women who smoke.

The number of cigarettes smoked daily and the degree of inhalation (none, slight, moderate, or deep) do not appear to have any statistical significance on pregnancy outcome; the important factor was whether the expectant mother smoked or not. Heavy smokers - those who smoke more than a pack a day - seem to run a slightly higher risk. But the differences between heavy and light smokers were not as striking as between smokers and non-smokers.

Women interviewed for the study included those who were treated following spontaneous abortions in three Manhattan hospitals from April, 1974 through August, 1976. To compare these women with women who did not abort, mothers who delivered babies after at least 28 weeks of pregnancy were selected from among those who were receiving prenatal care from the public prenatal clinics at one of the three hospitals. Each of these women was matched within two years for age at time of pregnancy with one of the women who aborted. The

(more)

SMOKE (CONT'D)

mean age of the two groups was nearly identical, 26.5 years for those who aborted versus 26.1 years for the other group.

The occupational and income levels were slightly higher among the women who aborted. Fewer of them were on welfare. The investigators say that these differences in occupation, income, and welfare status should have worked to minimize the association between smoking and pregnancy outcome since smoking is associated inversely with social class.

The study was reported in *The New England Journal of Medicine*. The first author is Jennie Kline, Ph.D., of the Division of Epidemiology, Columbia University School of Public Health.

#

NEWS & FEATURES From NIH March 1978

WOODRAT MAY HAVE NATURAL RESISTANCE TO RATTLESNAKE VENOM

Biomedical researchers at Texas A&I University in Kingsville, Texas, have discovered that the woodrat, a common rodent in the Southwest, has a natural resistance to rattlesnake venom. The discovery may lead to a more effective treatment for human snakebite.

Snake venom research has been conducted for over three years at Texas A&I by a research group headed by Dr. John Perez. The research is done by participants in the Minority Biomedical Support Program funded by NIH's Division of Research Resources.

"This particular research has medical applications in that the anti-venom factors found in the woodrat could possibly be used in snakebite treatment once isolated and purified," says Dr. Perez.

The research project was prompted purely by accident when one of the scientists, Allan H. Chaney, observed that woodrats survived multiple rattlesnake bites. He also observed that in some cases the woodrats actually killed the diamondback rattlesnakes.

A formalized study has been made using 35 woodrats trapped in East Central Kleberg County, Texas. The animals were housed in individual cages in a 21°C (69.8° Fahrenheit) animal room. Pregnant females and injured or immature rats were not used. Twenty-four woodrats were selected, divided into four groups, and each group injected with doubling dilutions of rattlesnake venom.

The venom used in the process is gathered from rattlesnakes which are kept in glass-front cages in the laboratory on the A&I campus. The snakes vary in size, and many are captured in the South Texas area.

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RESISTANCE (CONT'D)

Most of the snakes come to A&I from the annual Rattlesnake Roundup held near Freer in Duval County. Many other snakes caught in the roundup are "milked" and their venom released. The captive snakes are usually milked every week and returned to their cages.

The results of the experiment indicated that woodrats are resistant to rattlesnake venom as shown by a high LD_{50} (lethal dosage--concentration of a drug necessary to kill 50 percent of the population involved in an experiment); this resistance was 140 times greater than control mice.

The woodrats used showed very little tissue damage or internal hemorrhage compared to white laboratory rats injected with equivalent amounts of venom per body weight, the researchers report.

"The natural resistance in woodrats is not surprising," says Dr. Perez, "since woodrats and rattlesnakes live in the same habitat--often in the same burrows. The carnivorous diet of rattlesnakes and cohabitation with woodrats are two possible reasons for the evolved natural resistance."

The scientists have also successfully transferred the antihemorrhage factor in the woodrats to white mice, thereby giving the mice protection against rattlesnake venom.

In a summary report written for the professional journal, *Toxicon,* Dr. Perez concludes:

"Since venom consists of many toxins and enzymes, the possibility exists that the combined action of purified antivenom, rattlesnake and woodrat sera (watery portion of an animal fluid) could be more effective in snakebite treatment. The nature of the factor(s) responsible for this resistance in

(more)

RESISTANCE (CONT'D)

woodrats is not completely understood. Preliminary results suggest that a naturally occurring protective factor is present in the woodrat which will not react visibly with venom in the precipitin reaction. Further elucidation of the chemical nature of the antilethal factor(s) is necessary for studying the nature of inhibition."

Participating in the project were undergraduate researchers Eduardo Cantu, Noelia Cavozos, and Vivian Garcia.

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RESISTANCE (CONT'D)

The lightning thrust of a Western diamondback rattler holds no terror for the Texas woodrat. Scientists at Texas A&I University have determined that woodrats are immune to rattlesnake venom. The research is being done by participants of the Minority Biomedical Support Program, funded by NIH's Division of Research Resources. The investigators are now studying the nature of the antilethal factors for possible development of a more effective treatment for snakebite.
(NIH Photo #1608)

#

NEWS & FEATURES From NIH

March 1978

NEI WILL STUDY SAFETY OF INTRAOCULAR LENS IMPLANTATION

The first phase of a study to evaluate the safety and effectiveness of intraocular lens implantation, a procedure in which a plastic lens is placed in the eye after removal of a cataract, has been announced by NIH's National Eye Institute (NEI).

J. Robb Associates, Inc., a Texas-based organization which specializes in the application of statistics to health care evaluation and planning, will examine records of ten to 15 ophthalmologists who have performed lens implantation on large numbers of patients.

Under the direction of Jay H. Glasser, Ph.D., a biostatistician, J. Robb Associates investigators will first determine whether a sufficient number of comparable and adequately documented cases from these physicians' records are available for study. An NEI contract has been awarded to fund this part of the study which is projected to last one year.

If the available information is judged adequate for a definitive study, a complete analysis of the physicians' records will be carried out. This will involve measuring the frequency of intraocular lens complications, determining what factors were related to success and failure, and comparing the outcome of this procedure with alternative methods of cataract surgery and optical rehabilitation of cataract patients.

In cataract, the eye's natural lens becomes opaque and interferes with vision. Since the early 1970's, an increasing number of ophthalmologists have been using intraocular lenses to replace the natural lens which is removed in cataract surgery. The NEI estimates that more than 300,000 cataract operations are performed each year; 10,000 of these involve implantation of an intraocular

(more)

IMPLANTATION (CONT'D)

lens.

Intraocular lenses free those who have undergone cataract surgery from the need to wear special eyeglasses, which may be thick and heavy and cause significant image distortion and magnification. The implanted lenses also do not require the daily insertion, removal, and cleaning that are necessary with hard or soft contact lenses. In particular, many elderly people may find contact lenses difficult to manipulate and uncomfortable to wear.

On the other hand, it is possible that potentially serious complications which occur in only about five percent of cases of conventional cataract surgery, such as edema of the cornea and retina, may be more frequent following lens implantation. There may also be unknown, long-term complications.

As a result of accumulating reports of complications, some of which appear linked to "inadequate quality control and manufacturing practices," HEW's Food and Drug Administration (FDA) announced new regulations on November 8, 1977, that limit all intraocular lenses to investigational use only. In the future, only lenses that are adequately tested and proved safe and effective will be approved by FDA for general marketing.

According to NEI Director Carl Kupfer, M.D., "In view of the continuing controversy surrounding intraocular lenses, we hope that this study will provide useful information for evaluating the safety of intraocular lenses and for guiding ophthalmologists in their future use."

#

SIDS PROBABLY HAS NO SINGLE CAUSE

Tantalizing clues are becoming more numerous but a big breakthrough to explain the Sudden Infant Death Syndrome (SIDS) continues to elude scientists. In fact, there is increasing evidence that there is no single cause of SIDS.

SIDS, also known as "crib death," claims between 7,500 and 10,000 babies each year. It is the leading cause of death in the United States between the ages of 1 and 12 months, occurring two to three times for every 1,000 live births. Death usually occurs during sleep, suddenly, quietly, and unexpectedly.

New research findings have persuaded most scientists that SIDS babies are not the healthy infants before death that they were once believed to be.

Dr. Eileen G. Hasselmeyer, Chief of the National Institute of Child Health and Human Development's (NICHD) Pregnancy and Infancy Branch and co-chairperson of the DHEW Interagency Panel on SIDS, says that there is now a consensus among those working on the problem that SIDS babies have subtle anatomic and physiologic defects of a neurologic, cardio-respiratory and/or metabolic nature.

Instead of one causative factor, Dr. Hasselmeyer explains, a number of developmental, environmental, and pathological factors are probably involved. Under a complex set of circumstances not yet understood, these factors interact and set up a sequence of events that produces a sudden, unexpected, and thus far unexplained infant death.

Some possible explanations of this process were aired at a recent three-and-one-half day research reporting workshop for NICHD grantees and contractors working on the problem of SIDS.

More than 100 conferees including some from Australia, England, Italy,

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SIDS (CONT'D)

and Canada gathered to review and discuss SIDS related information, theories, and data that have emerged since a similar workshop was held in June, 1975. Pediatricians, pathologists, obstetricians, biochemists, anatomists, and parents of SIDS victims were among those attending.

The conferees were able to agree that several potentially useful indicators of babies at high risk for SIDS may have been identified, but that additional research is needed to define and refine these indicators before mass screening programs to identify babies at high risk for SIDS could be started.

Among the specific indicators that may be useful in identifying high risk babies are nine developed by Dr. Richard Naeye of the Milton S. Hershey Medical Center of Pennsylvania State University College of Medicine. From autopsies of 130 SIDS victims, Dr. Naeye has found nine factors which appear to affect the frequency of SIDS; he used these factors to construct a SIDS risk index. The nine factors are: maternal anemia, cigarette smoking, few visits for medical care during pregnancy; preterm delivery; lymphocyte infiltration into the mucous lining of the uterus; abnormal insertion of the umbilical cord into the placenta; blood type B in the infants; persistent brain dysfunction in the newborn; and high housing density for the involved family. The more of these factors found in the prenatal history, the higher the risk for SIDS appears to be.

Dr. Naeye said that the greatest use of such a risk index would be in screening for infants at high risk who could then be intensively studied by methods more specifically directed toward the mechanisms likely responsible for death.

(more)

SIDS (CONT'D)

These specific mechanisms are not yet fully understood, however. In the light of epidemiological research and autopsy findings, several theories have been proposed. These include:

* apnea - Sleep apnea, the temporary cessation of breathing during sleep, occurs in most newborns. However, repeated, prolonged (generally defined as more than 10 seconds) periods of apnea may be correlated with SIDS.

* laryngospasm - Death may be caused by an abrupt interruption of breathing resulting from an laryngospasm. Such a spasm may be caused by anatomic or biochemical defects in the infant or other unknown factors. The recorded cries of normal babies and of infants who later became SIDS victims are being compared to see if any differences can be detected which would indicate variations in laryngeal structure between the two groups.

* defective or low levels of phosphoenolpyruvate carboxykinase in the liver (PECK) - This enzyme is essential in the metabolism and synthesis of carbohydrates. Since some SIDS victims have been found to have lower-than-normal PECK levels, hypoglycemia has been proposed as a cause of death.

Research on these and other suggested causes of death is continuing. Epidemiological surveys, autopsy findings, behavioral observations, and studies of siblings of SIDS victims are among the approaches being taken.

Two groups of infants--siblings of SIDS victims and survivors of "near miss" episodes--are foci of special interest. By studying these two groups, investigators hope to detect physiologic or metabolic differences between normal infants and infants who die of SIDS. Such studies could determine if there is a genetic basis of SIDS and identify possible anatomic, physiologic,

(more)

or behavioral differences which could serve as "markers" of high risk infants.

Specific differences have been found in the behavior of siblings of SIDS victims and siblings of infants who do not die during infancy. SIDS siblings have been found to be less mature in their reactions to social visual stimuli upon awakening; they smile less often, take longer to learn to "tune out" environmental noise during sleep, and are more irritable and less consolable. The SIDS siblings were also found to be less adept at defensive maneuvers such as ability to use their hands to remove an obstruction that partially blocks their air passages. These findings may reflect behavioral manifestations of underlying physical abnormalities in these children, or they may indicate different nuturing techniques in their families, according to Dr. Lois Black Henning at the State University of New York Upstate Medical Center, who conducted the research.

"Near miss" infants--those who have stopped breathing and needed external stimulation to re-start respiration--are also the object of several research projects. "Near miss" episodes, which usually occur during sleep and often result in the infant turning blue or very pale and becoming limp, are of interest because of shared characteristics with SIDS. Many scientists believe that some of these "near miss" events would have resulted in death had the children not been revived. Some children have more than one of these episodes, and some do, indeed, later die of SIDS. Infants who survive a "near miss" are considered to be at high risk for SIDS and are often put on home monitors which alert the parents if the child stops breathing. The need for and efficiency of these monitors is still being debated; research is continuing on these questions.

(more)

SIDS (CONT'D)

Another important aspect of SIDS research is the study of normal babies. Until respiration and heart function, biochemical activity, and metabolism is better understood and described in the normal infant, it is difficult to ascertain what is abnormal in the SIDS victim.

Primary responsibility for Federally-sponsored SIDS research is placed with NICHD. During fiscal year 1977, the NIH Institute obligated an estimated $9.7 million to support more than 110 research projects related to SIDS.

#

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PORTFOLIO — NATIONAL INSTITUTE ON AGING
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MAR 21 1978
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Live Human Cell Bank Established For Aging Research

Photo courtesy of J.E. Johnson, Jr., NIA Gerontology Research Center

APRIL 1978

NATIONAL INSTITUTE ON AGING CULTURED-CELL REPOSITORY

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Cover photo: Scanning electron micrograph of IMR-90 cells shown at magnification of 15,000. IMR-90 and IMR-91 cells are now available to researchers conducting investigations on aging. (NIA Photo #CP-1)

Introduction

In recent years it has become increasingly important to understand the biological aging processes of man. Because cells and extracellular substances are organized into what we recognize as tissues and organs of the body, studies at the cellular level offer great opportunity to advance our knowledge of human aging and ultimately improve the health of our older citizens. Recognizing the need for such research, the National Institute on Aging has developed a unique new resource for scientists conducting gerontological studies--a bank of live human cells in culture. Through its contract with the Institute for Medical Research (IMR) in Camden, New Jersey, the NIA establishes, characterizes, stores and distributes standard and genetically-marked human cell lines for aging research.

Pertinent Cell History and Directions in Cell Research

In the last quarter century, scientists have provided us with the information and technology necessary to grow and study live human cells in culture (in vitro). Human cell culture science has already had a profound effect on many areas of biological research including immunology and genetics.

It has become increasingly clear that observations of cultured replicating or multiplying human cells are vital to the study of human aging processes. In the 1960's, cell biologists first noted an apparent inverse relationship between the total number of times a cell divides in culture and cell donor age. In other words, the younger the donor, the greater the number of cell divisions in culture. Scientists also observed that cultured cells of a young individual begin dividing or initiate their primary phase of proliferation much sooner than do the cells of an old person. This period of time from placement of cells in the culture medium to an initial division is termed the latent period. The length of the latent period seems to be determined by donor age.

Many years ago, two separate studies showed that cells taken from chicken embryo heart tissue remained alive in culture for inordinate amounts of time (up to 34 years). Partly because of these studies, investigators have long sought normal cultured human cells capable of indefinite or prolonged proliferation. In the last two decades, it has been shown that normal human cells eventually stop dividing in culture and that this process of proliferation is not infinite.

Current investigations focus on the relationships between the aging process and cell differentiation, cell division, loss of normal cell function and cell "death". Scientists hope to determine how these occurrences affect the biological aging process and how, in turn, the aging process affects cell behavior. We want to develop methods for early detection of cellular aging and try to control or reverse adverse changes which take place.

Special Resources of the Cultured-Cell Bank

The respository at the Institute for Medical Research houses four types of cultured human cell lines. These include: 1) human cell lines derived from normal individuals (from fetal to old age); 2) strains of cells derived from individuals with abnormal growth disorders which feature symptoms of accelerated aging, such as progeria; 3) cells derived from originally normal lines transformed by virus infection and 4) cell lines derived from individuals at high-risk to cancer. We can obtain detailed information on *in vitro* cellular aging by studying cells which range in activity from a normal rate of proliferation to an accelerated rate of division to the never-ending, cancerous form of cell growth.

Several years ago the National Institutes of Health supported development of a human diploid (containing 46 chromosomes) cell strain which subsequently became the "cell line of choice" for aging research. This cell line, named WI-38, has since become relatively limited for purposes other than vaccine manufacture. Realizing the need for a human diploid cell line for scientific research, the NIA commissioned IMR to establish a new line of cells which would closely resemble WI-38. IMR-90 is just such a line. It was derived from female embryonic lung tissue and closely parallels WI-38 to provide interchangeability with the original aging line in ongoing experiments. The extensive frozen stock of IMR-90, combined with a carefully planned distribution protocol, enhances long-term availability of these cells to research scientists.

Under NIA direction, the Institute for Medical Research has also established another new "normal aging" cell line called IMR-91. Derived from human male embryonic lung tissue, IMR-91 will also be available on a long-term basis. In the near future animal cell lines, appropriate to aging research, will be made available through the NIA-IMR cell bank.

At IMR cultured human cells are frozen in liquid nitrogen at -316 degrees F. Cells are frozen when they are at low passage--still relatively "young" with the promise of many more divisions for the researcher to observe before the cells cease dividing in culture. Advantages to investigators using cells from this repository include the assurance of a well-characterized human cell line which has been established and maintained in a germ-free environment. From the time of biopsy (surgical removal of tissue specimens) to the time cells are frozen, they are handled in a carefully controlled, sterile environment. Cells are checked repeatedly for the presence of mycoplasma, possibly the most evasive cell culture contaminant of all.

Cell Banking Procedure--from Biopsy to Freezing

At the Camden facility, cultured cell lines are usually established from skin/tissue biopsies 3-4 mm in diameter. Immediately after a specimen has been removed from the donor it is placed in a tube filled with culture medium rich in essential nutrients. In addition, antibiotics (usually Penicillin and Streptomycin) are added to the medium to sterilize the specimen and keep it free of contaminants. The vial is then sealed and hand-carried or air-mailed to the repository.

From the time biopsies arrive until daughter cells are frozen, all procedures are performed in a sterile environment. The rooms in which cells are handled and stored are called laminar air flow units or "hoods". All "hood" air is filtered meticulously to avoid contamination. In addition, lab technicians must wash their hands and arms thoroughly, wear surgical caps and gowns and refrain from talking while in the sterile rooms. Equipment used to handle the cells is also sterilized, usually by autoclave.

Once unpackaged, the tissue specimen is washed several times in new culture medium which also contains antibiotics. Using two scalpels in a criss-cross fashion, the lab technician cuts the tissue into tiny chunks which are then placed on the floor of a (T-25) flask. The container is then inverted so that the tissue rests on the flask ceiling. New antibiotic-containing medium is placed on the opposing side to humidify the flask. After an hour, when the tissue adheres securely, the technician rotates the container very slowly so that this medium covers the specimens. The flask is then capped and placed in an incubator room maintained at 98.6 degrees F or human body temperature. In approximately five days cells of the primary culture migrate out from the tissue specimens and begin dividing. At the end of another week, scientists use an inverted microscope to determine if these dividing cells have completely covered the floor of the flask. This total occupancy of available growing space is termed confluence. When confluence is attained, it is time to harvest the primary culture. After pouring off any remaining medium, a pancreatic enzyme called trypsin is added to the flask to loosen the cells. Technicians use a pipette with a squeeze bulb tip to slosh the cells until a single cell suspension is obtained. Once in this form, a sample portion of the cells can be counted and population doublings determined. From each passage or harvest of cells approximately 500,000 daughter cells are planted and a new passage is seeded. At the end of each harvest a certain portion of cells are centrifuged, placed into ampules which are fired shut and then cooled at the rate of 1-5 degrees/minute before freezing in liquid nitrogen.

Effect of Cell Resource Development

It is hoped that by developing this cultured-cell bank resource, we can speed our research efforts into the human aging processes. Hundreds of experiments which would be impossible to perform on man can now be carried out on live cells grown from small slivers of human skin and tissue.

In the near future, NIA hopes to provide two additional services for cell biologists conducting aging research. Initially, NIA will establish a facility for purposes of mycoplasma detection. Mycoplasma are tiny organisms, smaller than bacteria but larger than viruses, which often contaminate cell cultures. If undetected, the evasive mycoplasma tend to skew or invalidate research results. Once a mycoplasma testing facility is underway, researchers can mail in samples of their cultured cells for mycoplasma detection.

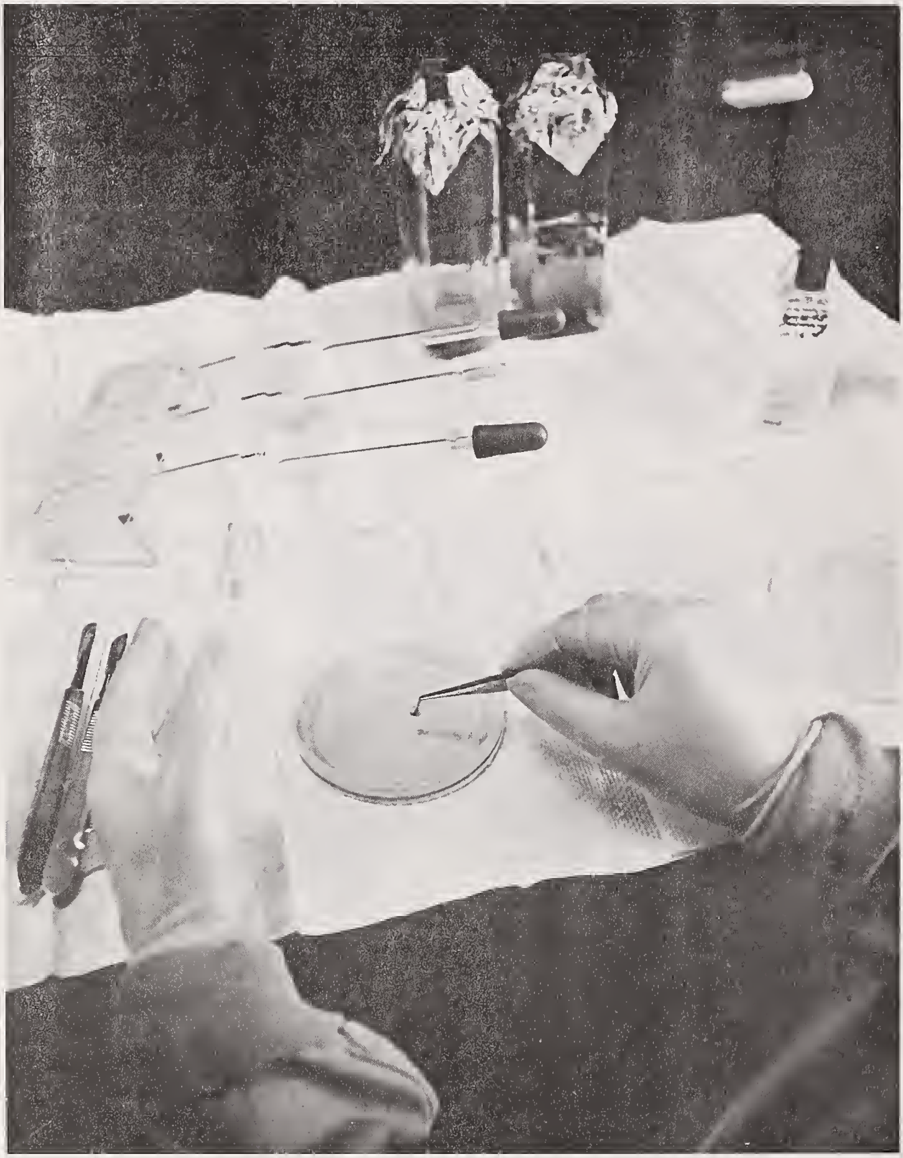
Secondly, the NIA will consider a cell line identification service. For this type of service, a facility will be set up to properly identify cell lines by closely examining small samples. This will aid researchers to sort out problems of cell line mix-ups and the like.

While the NIA maintains the only human cell repository for aging research, the National Institute of General Medical Sciences supports a cultured-cell bank for the study of genetic disorders. The Division of Research Resources administers an NIH-supported cell resource and banking effort which provides research materials for those studying viruses and bacteria.

For further information on the resources of the NIA-IMR cultured-cell repository contact: Dr. Warren Nichols, IMR, Camden, New Jersey, (609) 966-7377, ext. 123; or Dr. Donald Murphy, NIA, (301) 496-5534.

Many of the cell lines established and maintained at the NIA/IMR cell bank are derived from skin biopsies measuring 3-4 mm in diameter. Dr. Warren Nichols, Director of this repository, demonstrates the "punch" biopsy method often used for this purpose. (NIA Photo #1)

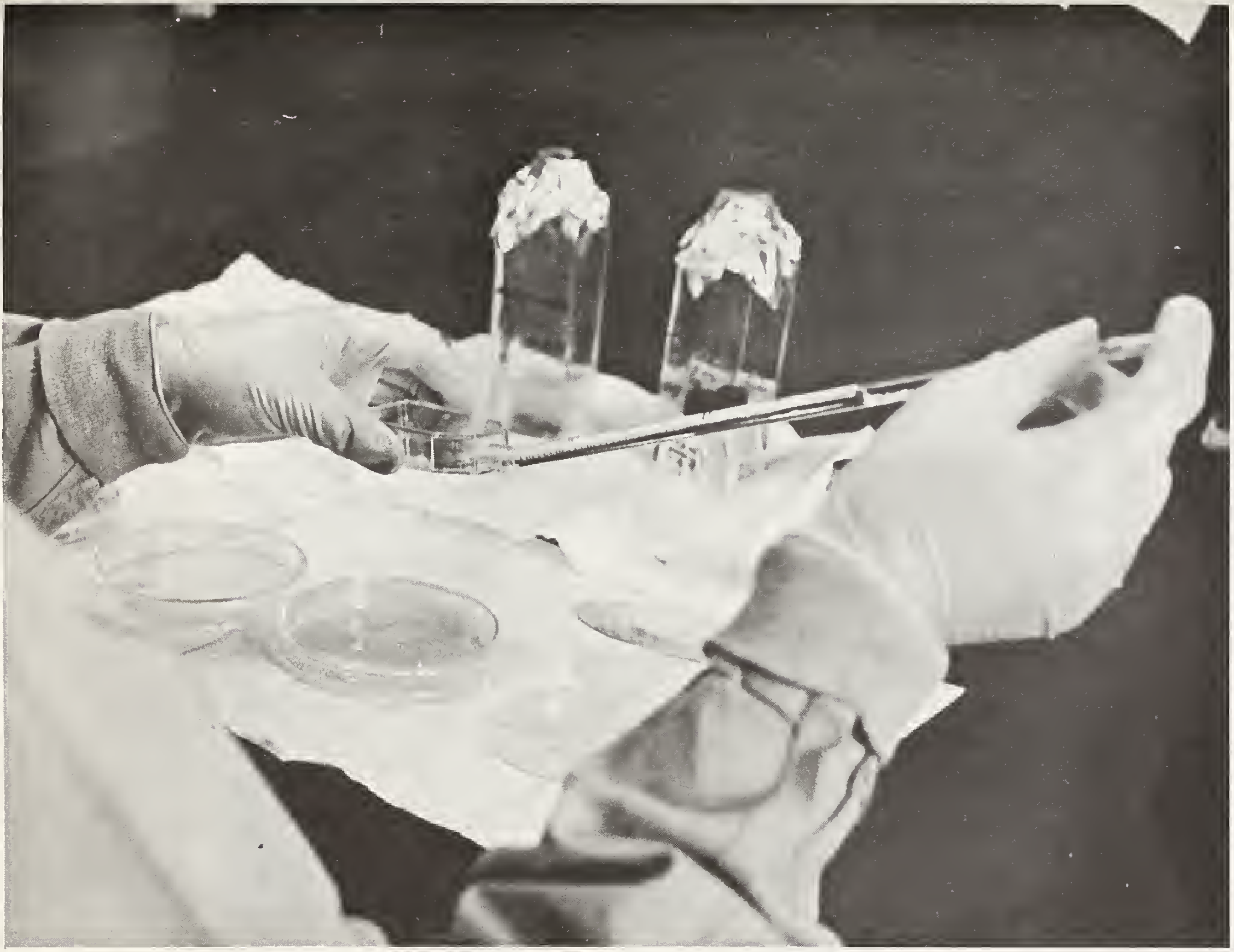
All procedures, from unpackaging of the biopsied tissue specimens to freezing, are performed in a sterile environment. This plastic enclosure or "hood" is kept contaminant free by filtering all incoming air and by pushing all existing air down and out over the floor of the room. (NIA Photo #2)



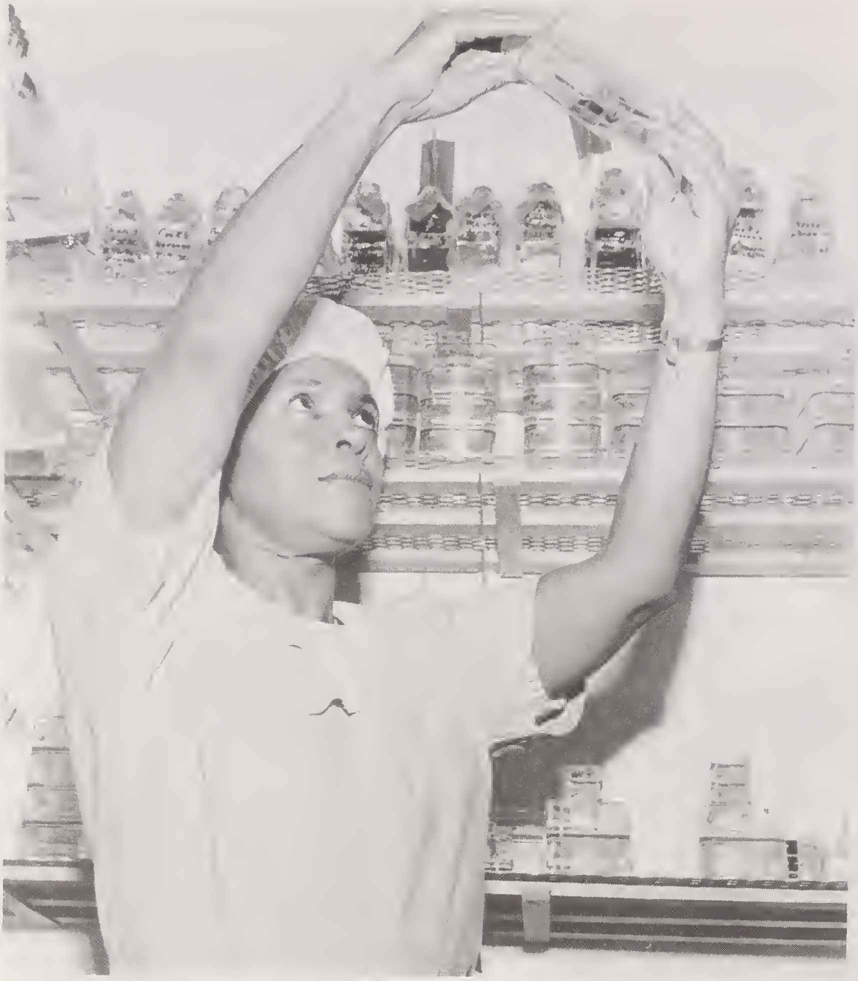
New tissue specimens are washed in clean culture medium containing antibiotics to keep them free of contaminants. (NIA Photo #3)

Once the specimen has been washed thoroughly, a technician cuts it into tiny pieces using two scalpels in a criss-cross fashion. Scientists employ this technique to avoid tearing the tissue. (NIA Photo #4)

The small chunks of tissue are then carefully placed on the floor of a flask (T-25). This step constitutes the planting of the primary culture. (NIA Photo #5)



The technicians uses a pipette to place a small amount of new culture medium on the side of the flask opposite the tissue specimens. This medium humidifies the flask while the tissue chunks adhere to the surface. (NIA Photo #6)



After about an hour, the technician rotates the flask slowly so that the medium covers the pieces of tissue. The "seeded" flask is now capped and placed in this incubator room maintained at human body temperature. (NIA Photo #7)

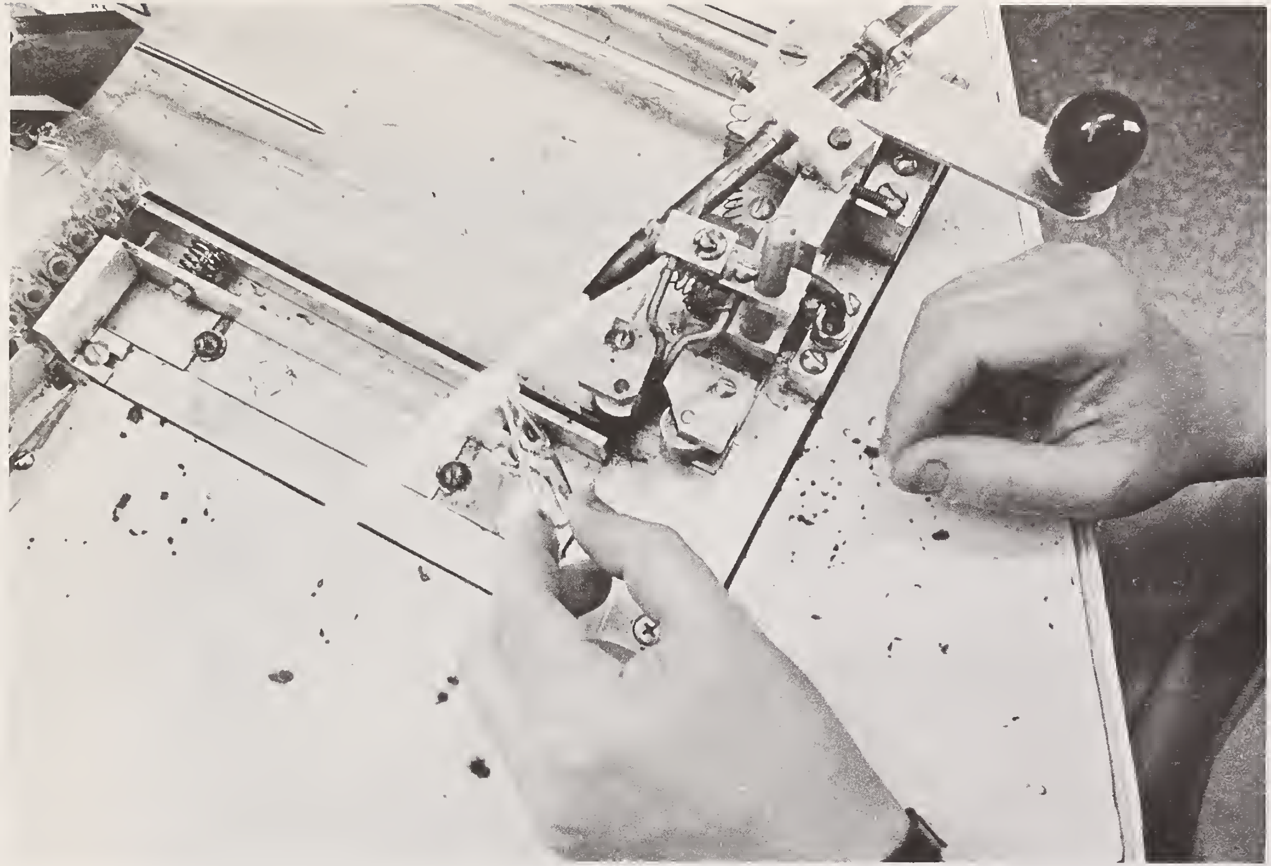
In approximately 5 days cells of the primary culture migrate out and begin dividing. In this photo, cells have been fixed and stained to simulate this initial phase of division. (NIA Photo #8)

At the end of another week, scientists use an inverted microscope (with light source above the specimen and eyepiece beneath it) to determine if dividing cells totally occupy the floor of the flask. This total occupancy of available growing space is termed confluence. (NIA Photo #9)

Once confluence is attained, it is time to harvest the culture. After pouring off any remaining medium, trypsin enzyme is used to loosen the cells. Technicians then use a special pipette to slosh the cells until a single cell suspension is obtained. Once in this form a sample portion of the cells can be counted. (NIA Photo #10)

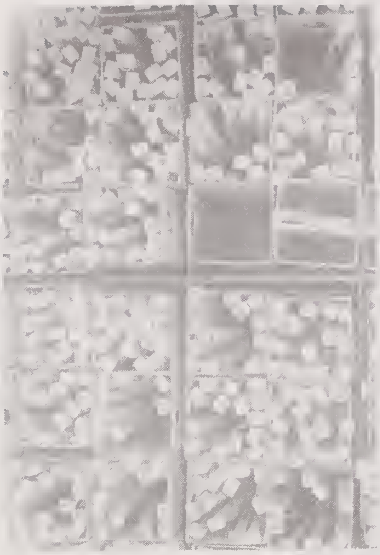
In a separate step, cell population doublings are determined.
(NIA Photo #11)

From each passage (harvest) of cells approximately 500,000 daughter cells are planted and a new passage is seeded. Also at the end of each harvest a certain portion of cells are centrifuged and placed into ampules with a syringe. Each ampule is filled with approximately 500,000 cells. (NIA Photo #12)



To allow for efficient sealing a gas flame is used to fire the filled ampule shut. The ampule is then cooled at the rate of 1-5 degrees per minute. (NIA Photo #13)

Filled ampules are then loaded or snapped into metal canes.
(NIA Photo #14)



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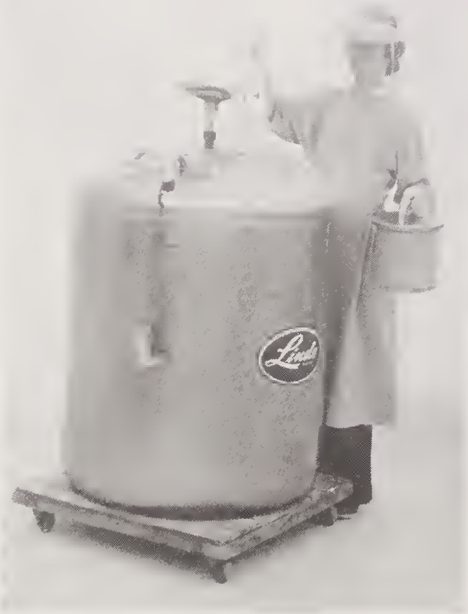

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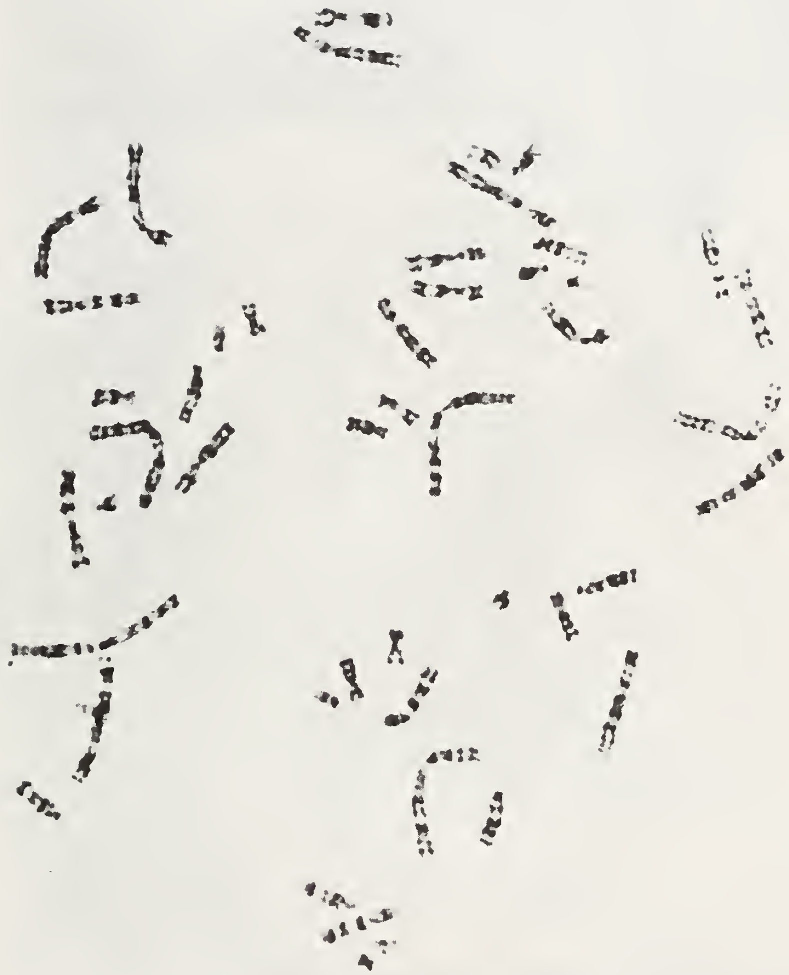
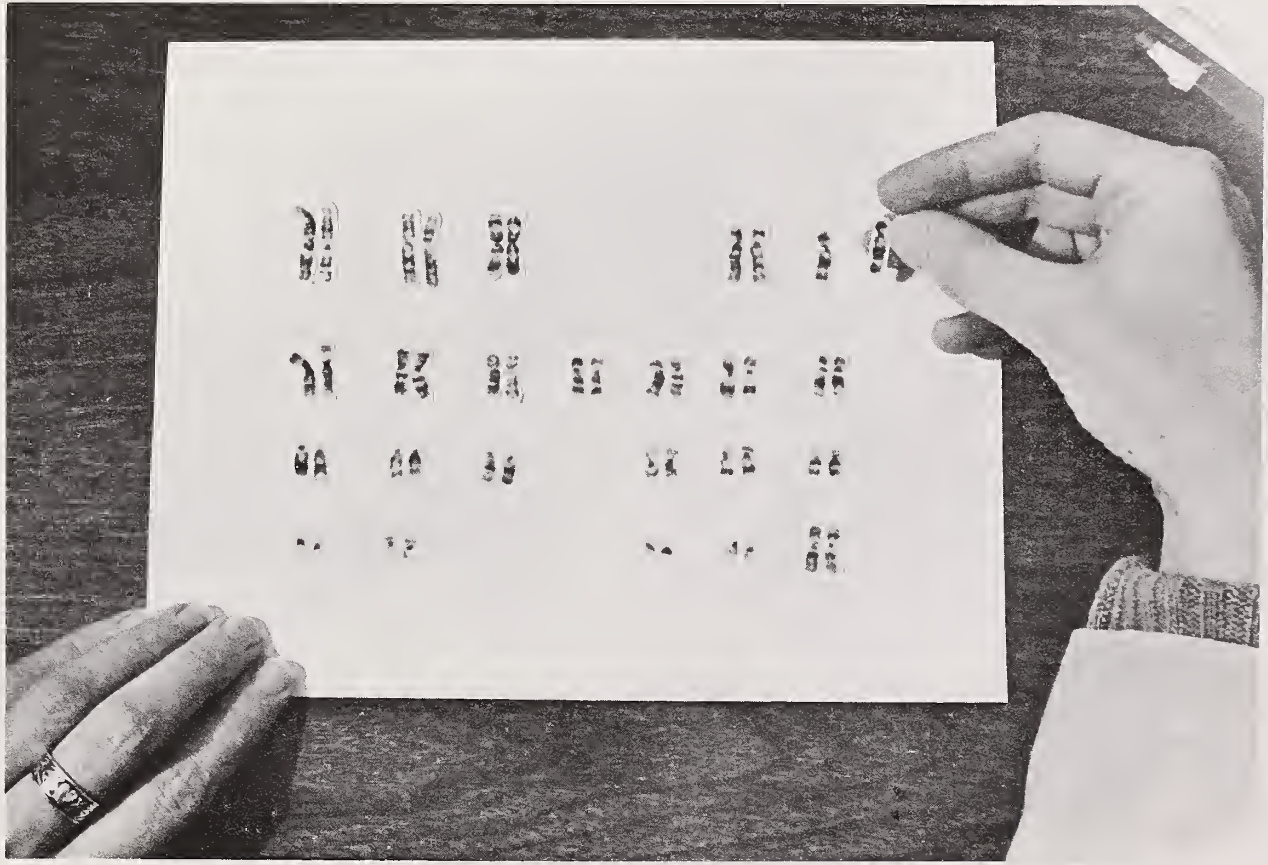
Figure A shows the canes placed in hanging containers which are then, as shown in Figure B, stored in liquid-nitrogen freezers. (NIA Photos #15A, 15B)

Technicians must wear protective gloves and face gear when retrieving ampules from the freezer. Occasionally an ampule will explode as it undergoes rapid temperature changes. (NIA Photo #16)

It is often desirable to do a chromosome analysis or genetic study of cells in the repository. To do this karyotype analysis, the technician fixes and stains the cells on a slide for microscopic examination. (NIA Photo #17)



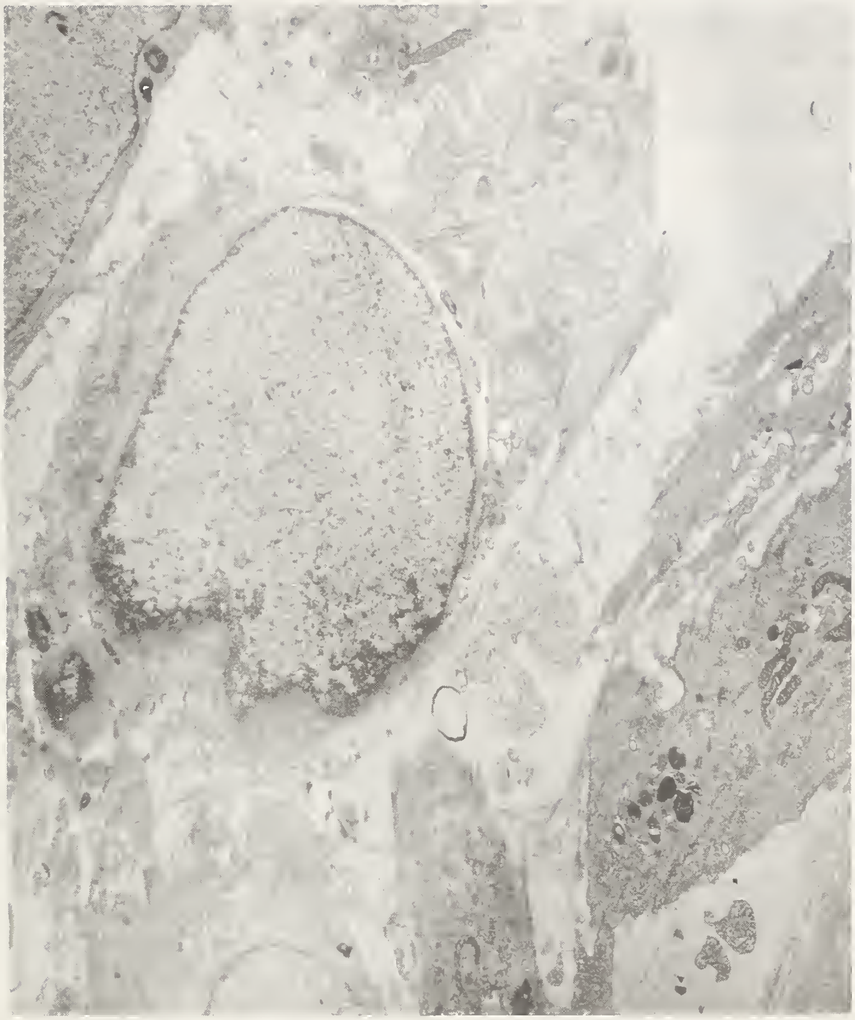
This photo shows the random occurrence of the chromosomes as seen through the microscope. (NIA Photo #18)



By looking at the banding and by comparing length of these chromosomes, it is possible for scientists to match or couple them for study,
(NIA Photo #19)

All cell lines maintained at the IMR facility are carefully observed and growth patterns and growth characteristics documented. (NIA Photo #20)

This data is logged in and charted by scientists and then stored by computer for easy retrieval. (NIA Photo #21)



Transmission electron micrograph of IMR-90 cells. It is expected that IMR-90 will eventually replace the WI-38 cell line in ongoing gerontological cell research. (NIA Photo #22)

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May 1978

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WIFE'S BREAST REMOVAL MAY STRAIN MARRIAGE

The psychological, psychosomatic, and sexual responses of husbands to their spouses's mastectomy can precipitate a marital crisis of profound proportions.

Supported in part by NIH's Division of Research Resources, investigators at UCLA found that the removal of a wife's breast because of cancer generally indicated four focal points in the husband's adjustment. These were: involvement in the decision-making process, the frequency of hospital visits, the resumption of sexual relations, and the man looking at his partner's body after surgery.

As reported in the May 1978 issue of the *American Journal of Psychiatry*, their study sample consisted of 30 husbands, and one man who was cohabitating, whose partners underwent a mastectomy. Half of the sample was recruited through Women for Women, a self-help mastectomy recovery group, and the rest through referral from the American Cancer Society. The age range was 34-74, 29 of the men were white, one was black and one oriental. Average annual income was $20,000, and most men had at least some college education. The average length of marriage was 23 years, and the average amount of time post-mastectomy was 22 months.

The men completed a personality inventory, a marital adjustment test, and eight pages of open- and close-ended questions dealing with their perception of their partner's emotional and behavioral state before and after mastectomy. In addition, multiple aspects of the men's own emotional and behavioral condition were assessed.

As a group, the men were found to be generally stable, with a marked tendency to extroversion. They generally viewed their relationship as being more positive than they thought their spouses would: 35.5 percent rated their

(more)

MARRIAGE (CONT'D)

relationship as "excellent" but only 30 percent thought their spouses felt the same. None of the men rated their relationship as "very unsatisfactory" or "totally unsatisfactory."

The data showed 56.6 percent of the men were involved "to a very considerable extent" or "quite an extent" in the decision-making process before the surgery; 43.3 percent felt themselves to be involved "very little" or "not at all." The men who had been most involved rated their sexual satisfaction higher than the less involved both before and after mastectomy, an important finding.

In general, however, the men indicated that sexuality and intimacy were severely stressed and often negatively altered after surgery. Sexual frequency decreased in all respondents, and 16 percent felt that mastectomy had reduced their wife's orgasmic potential. Six of the men had not seen their partner unclothed since the surgery. The questionnaire did not determine whether this was their own or their partner's preference, but it is a potentially crucial question in resumption of intimacy. The eight men who rated their pre-mastectomy sexual relationship as "totally satisfactory" applied the same rating to their relationship after surgery, but the rest indicated a diminution of satisfaction.

Two of the men were infrequent visitors during their spouse's hospitalization. They required a maximum of emotional support from others during the post-surgical period. The remainder were daily visitors save for one respondent who did not answer the question. Forty percent of the men reported nightmares and sleep disturbance and 27 percent loss of appetite in the immediate post-surgical

(more)

MARRIAGE (CONT'D)

period until discharge. Forty-two percent felt their ability to work or concentrate had been similarly affected during this time.

The general picture which emerges is basically encouraging. Most men coped well with the stresses which the mastectomy imposed and their relationship remains sound. A smaller sub-group, however, was distressed, remains distressed, and reported a continued downward spiraling in the quality of their relationship.

The findings point to the husband's involvement in the decision-making process as the logical focal point in the primary prevention of damaging after-effects. A husband who chooses to remain uninvolved seems particularly at risk and in need of advice.

Given the frequency of this procedure (approximately 200,000 mastectomies per year) and its potential trauma for both partners, the investigators, Drs. David Wellisch, Kay Jamison, and Robert Pasnau, feel that expert marital and sexual counseling should be available and encouraged. Their investigations, which earlier examined the wife's adjustment, were conducted at the University of California, Los Angeles, Department of Psychiatry, Center for Health Sciences.

#

NCI STUDIES HORMONE RECEPTOR PROTEINS IN BREAST CANCER

The presence of hormone receptor proteins in breast cancer tissue may be a useful indicator of the kind of therapy that would be most effective in treating the disease, according to Drs. Joseph C. Allegra and Marc E. Lippman and their co-workers in the National Cancer Institute's Division of Cancer Treatment and Howard University's Cancer Research Center.

They presented their findings of a study with breast cancer patients on April 4 at the 14th Annual Meeting of the American Society of Clinical Oncology in Washington, D.C.

Hormone receptors, which selectively bind specific hormones, are being studied in an attempt to discover which breast cancers are hormone dependent and, therefore, might be controlled by hormonal therapy.

Hormone therapy often is used when breast cancer recurs some time after surgery.

The estrogen receptor protein was the first of the hormone receptors found in breast cancer tissue. Since then several other hormone receptors have been discovered.

Drs. Allegra and Lippman and colleagues analyzed the breast tissue of 329 breast cancer patients for four hormone receptors: estrogen and progesterone, female hormones; androgen, a male hormone that is present in minute amounts in females; and glucocorticoid.

Estrogen receptors were found in 53 percent of the patients, most of whom were postmenopausal. Of these estrogen receptor-positive patients, 65 percent responded to hormone therapy.

Only nine percent of patients without the estrogen receptor responded

(more)

RECEPTOR (CONT'D)

to hormone therapy.

Patients with both the estrogen and glucocorticoid receptors had a higher response rate of 83 percent.

Patients with estrogen and progesterone receptors showed a trend toward an increased response rate, but the comparison was not statistically significant.

The presence of androgen receptor with the estrogen receptor was of no significance.

Surprisingly, the presence or absence of hormone receptors correlated with patients' response rates to chemotherapy as well as to hormone therapy.

Seventy of the patients who were tested for hormone receptors underwent chemotherapy. Of 45 patients who were estrogen receptor negative, 34 (76 percent) responded to anticancer drugs.

Of the 25 estrogen receptor positive patients, only three (12 percent) responded to chemotherapy.

#

NIH SEEKS ROLE OF COLLAGEN IN TISSUE FORM, FUNCTION

An NIH scientist has described research that may partially bridge the wide gap between scientific knowledge of how genes control the production of proteins and an understanding of how those protein molecules actually become organized into body tissues and organs.

Citing research from many laboratories in the United States and abroad, Dr. George R. Martin described how collagen Type I, the most abundant protein in the body, appears to serve as a biological rope along which cells in a developing embryo crawl into appropriate positions. After the cells begin organ development, the pathways are closed. He also described other kinds of collagen and their functions.

Speaking at an NIH Science Writers Seminar on May 17, 1978, in Bethesda, Maryland, Dr. Martin noted that most human cells, except blood and brain cells, exist in a matrix or web of collagen fibers. Cells migrate by grabbing hold of one sticky collagen molecule after another. The collagen fibers are sticky as a result of "attachment proteins," also called "fibronectins," produced by the cells forming the various kinds of collagen.

Type I, a cable-like collagen, is found in skin, tendon and bone. Type II, found only in cartilage, forms resilient, elastic tissue. Type III collagen is in blood vessels, intestine, and smooth muscles. Type IV collagen is the principal component of the basement membrane that serves as a ground layer for the skin's epidermal cells, kidney glomeruli, and all mucous membranes; it also encloses blood vessles, nerve cells and nerve bundles. Other collagens exist: their exact roles are unclear.

(more)

COLLAGEN (CONT'D)

Dr. Martin, who is Chief of the Laboratory of Developmental Biology and Anomalies at NIH's National Institute of Dental Research, noted that early findings on collagen structure were made more than twenty years ago by Alexander Rich and Francis Crick in England, and G.N. Ramachandra in India. Subsequent important contributions on collagen chemistry and structure have been made by Drs. Francis Schmitt at MIT and Jerome Gross at Harvard, and by Drs. Karl Piez, NIDR, and Edward Miller and Paul Bornstein while at the NIH.

Evidence pointing to collagen's organizational role during embryonic life has been reported by many laboratories since the late 1950's, notably by Drs. Clifford Grobstein, now of the University of California in San Diego, and Elizabeth Hay of Harvard Medical School. In 1965, Drs. Stephen Hauschka and Irwin Konigsberg, working in Baltimore, showed that collagen was necessary for embryonic muscle formation. In 1975, Drs. M.C. Johnston and R.M. Pratt of the National Institute of Dental Research, NIH, described the role of a collagen matrix in the migration of cells from the embryonic neural crest of chick, rat and amphibia to form the mandible and other structures.

Collagen's organizational role does not end at birth, Dr. Martin said. If body tissue is injured, as in a cut or wound, the injured cells are activated immunologically to produce collagen and attachment proteins, permitting replacement cells to recolonize the site and restore the original architecture of the tissue. Dr. Martin referred to work in Dr. Russell Ross' laboratory at the University of Washington in Seattle that showed collagen's exacting role in such cell migration when replacement cells close a wound precisely without overgrowth.

While fibroblasts can attach to any collagen, epidermal cells bind and grow only on basement membrane collagen (Type IV). Dr. Martin noted that

(more)

COLLAGEN (CONT'D)

epidermal cells may use this collagen and its cell attachment protein to find their proper location in the tissues.

The finding of collagen attachment proteins or fibronectins was a major advance made by Dr. Robert J. Klebe while at Salk Institute in 1974. Drs. James A. Weston of the University of Oregon in Eugene, Kenneth Yamada of NIH's National Cancer Institute, and Richard Hynes at Massachusetts Institute of Technology, and their colleagues made related observations.

Dr. Martin said that fibronectins are lost from the surface of malignant cells in tissue culture; the addition of fibronectin restores normal cellular morphology, although the cells remain malignant. He described various collagen abnormalities that play a role in diseases such as diabetes, arteriosclerosis, and in rare conditions like relapsing polychondritis and Ehler's-Danlos disease. He suggested that collagen abnormalities may be shown to play a role in other disease states in the future.

#

MAJOR NUTRITION CONFERENCE WILL BE AT NIH, JUNE 19-20

Interest in nutrition has steadily increased in the past decade. Today all segments of the scientific community, Congress, and the public are concerned and involved in the progress and benefits of nutrition research.

Recognizing this awareness, the Nutrition Coordinating Committee (NCC) of the National Institutes of Health will sponsor a conference on "The Biomedical and Behavioral Basis of Clinical Nutrition: A Projection for the 1980's." The conference will be held June 19-20, 1978, at the National Institutes of Health campus in Bethesda, Maryland. Pre-registration for the conference, which will meet in the Masur Auditorium of the Clinical Center, is strongly recommended.

The purpose of the conference is to review biomedical and behavioral research in nutrition, to relate this research to current clinical practice, and to project the future frontiers of nutritional investigations and applications. The National Institutes of Health, the Food and Drug Administration, the Department of Agriculture, and the Department of Defense will present their ongoing research programs in nutrition, and six scientific panels will consider the following topics:

* "Genetic Disorders: Lessons for Clinical Nutrition"

* "Early Nutrition: Developmental Consequences"

* "Basic Biochemical Research: A Key to the Solution of Nutritional Disorders"

* "Nutritional and Environmental Practices: Consequences for Health"

* "Nutrition and Performance"

* "Nutrition and Behavior: Interactions"

(more)

CONFERENCE (CONT'D)

In addition, there will be a panel of Congressional staff chaired by Mr. Chris Hitt, and a consumer affairs panel headed by Dr. Gilbert Omenn. The June 20 session concerning the Federal, Congressional, and consumer aspects of nutrition research and education will be conducted by Dr. J. Michael McGinnis, Chairman of the HEW Nutrition Coordinating Committee.

"In this meeting we will seek to define the scientific basis for research in clinical nutrition, and make projections for the direction of biomedical and behavioral research in nutrition for the 1980's," said Dr. Donald S. Fredrickson, NIH Director.

The Nutrition Coordinating Committee is composed of representatives from the 11 institutes and two divisions of the NIH that conduct nutrition research. Located in the Office of the Director, the NCC coordinates and oversees the nutrition research programs at NIH.

Opening remarks at the conference will be presented by Dr. Fredrickson. Other speakers will include HEW Secretary Joseph A. Califano, Jr., FDA Commissioner Donald Kennedy, USDA Assistant Secretary Dr. Rupert Cutler, Senator George McGovern, and Dr. Rene Dubos.

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May 1978

NEWS & FEATURES From NIH

NIH'S P4 LABORATORY DESIGNED TO MEET HIGHEST STANDARDS

The first laboratory certified as a maximum containment facility for conducting recombinant DNA research has begun operations. NIH's National Institute of Allergy and Infectious Diseases (NIAID) made this announcement March 17, 1978, at a special press briefing held at the laboratory located on the grounds of the Frederick Cancer Research Center, Frederick, Maryland.

The new NIH P4 laboratory has been designed to meet the highest standards of physical safety set forth by the NIH guidelines. These regulations categorize experiments according to the potential risks involved and specify conditions and procedures devised as safeguards for conducting this research.

According to Dr. Richard M. Krause, Director of the NIAID, "the P4 laboratory will enable scientists to safely conduct experiments requiring the highest level of physical containment." Until now, no laboratory in the United States had been certified for maximum containment as stipulated by the NIH guidelines, which apply to all federally-supported recombinant DNA research.

The first experiments to be performed in the P4 facility will evaluate the potential risks involved in recombinant DNA research. Two virologists from the NIAID -- Drs. Wallace Rowe and Malcolm Martin -- will link together viral DNA from the mouse polyoma virus with the DNA from a bacterial plasmid and insert this recombined DNA into a weakened strain of *E. coli*. The bacteria -- with the recombined DNA -- will then either be injected into or fed to mice, so that the scientists can later search for evidence of infection in these animals by the viral gene. Before these experiments are begun, the facility will be run as a "dummy" laboratory for one week to test safety procedures.

Upon completion of the risk assessment studies, the P4 laboratory will

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be available to other NIH and visiting scientists who will conduct their experiments with the assistance of a trained staff.

The laboratory itself -- under negative air pressure -- is specifically equipped to prevent the escape of any microorganism into the environment. All experiments will be carried out in an elaborate system of enclosed, interconnected, gas-tight cabinets. Laboratory workers will reach into glove boxes containing shoulder-length, heavy rubber gloves attached to the sides of the cabinets to carry out their experiments. The cabinet system measures approximately 70 feet in combined length and is contained in a room of about 400 sq. feet. Before entering and leaving, all the cabinet line system materials and equipment must be either sterilized or disinfected.

Operated for the NIH by NIAID, the one-room laboratory is expected to function as one of three interim facilities to be set up pending completion of renovations for the National Biomedical Containment Laboratory which will also be located at Frederick, Maryland. The National facility, which will house both P4 and P3 laboratories, is not expected to be operational before 1979 or 1980.

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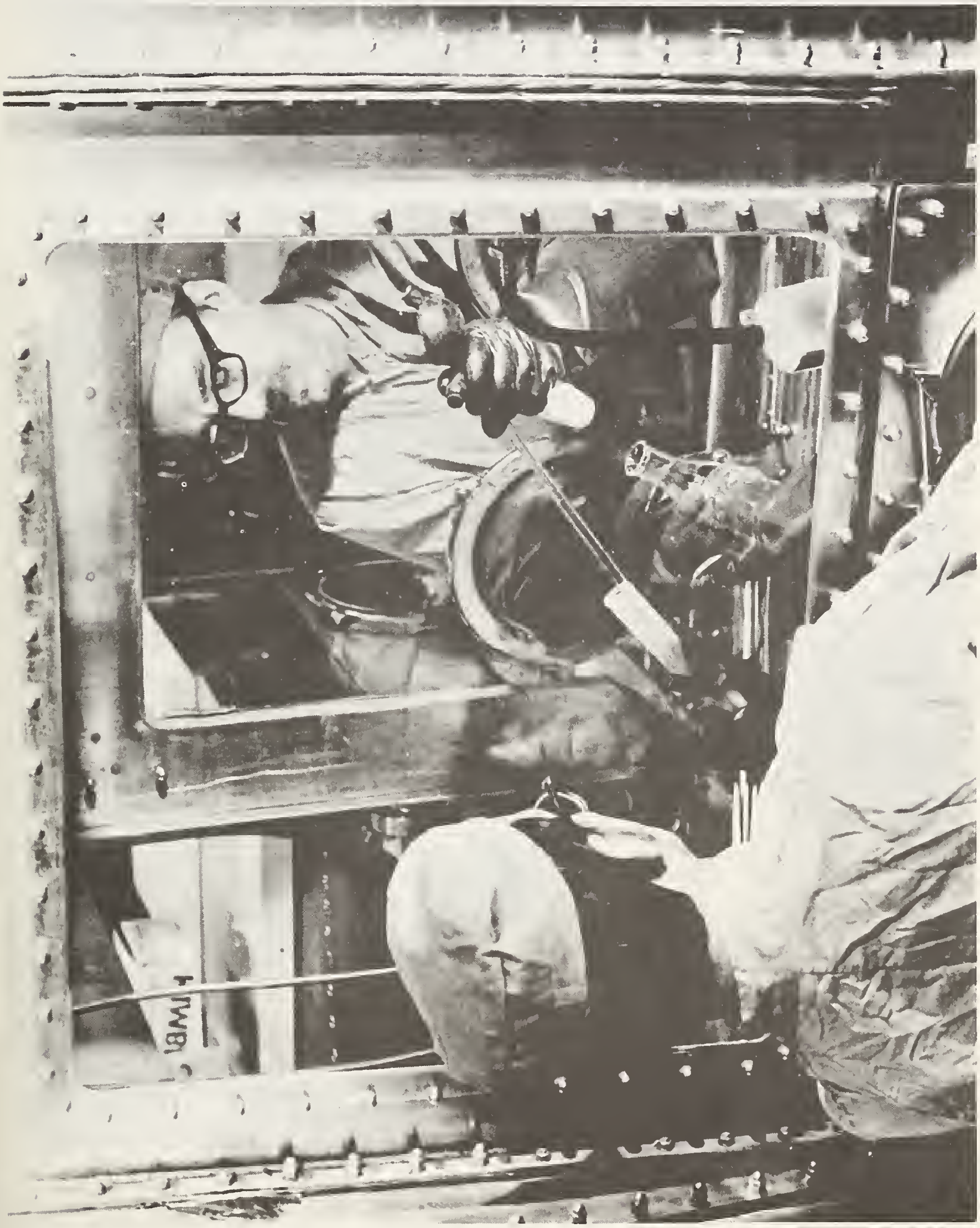
P4 LABORATORY (CONT'D)



Researchers use shoulder-length rubber gloves to move and control all the materials and tools in their experiments preventing direct contact between their hands and anything inside the cabinet system. The cabinet units are interconnected and allow for the free movement of materials within them. (*NIH Photo # 1609*)

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P4 LABORATORY (CONT'D)

Despite the limitations imposed by the heavy rubber gloves used in performing experiments in the National Institutes of Health P-4 laboratory cabinet system, skilled workers are able to make delicate adjustments on the microscope. A closed-circuit television system with the screen mounted above the researcher's head provides the means for viewing. The NIH P-4 containment facility at Fort Detrick in Frederick, Maryland is the first recombinant DNA research laboratory certified to meet the P-4 requirements set forth in the National Institutes of Health guidelines. (NIH Photo # 1610)

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COMPUTER MAY SOON AID INTERNISTS IN DIAGNOSIS

Sitting in front of a small computer terminal, a family physician in a remote Pennsylvania town provides information to a central computer in Pittsburgh based on a history and physical examination he has just obtained on a patient. The computer digests the information and begins asking questions of the physician concerning the patient. In the course of asking the questions, the computer will tell the physician what diagnoses it is considering and how the answers to the questions will help reach a final decision.

After several minutes, the computer provides its diagnosis for the physician.

If that sounds like something medicine is only dreaming about; guess again. Two professors at the University of Pittsburgh are well on the road to making it a reality. They call their system INTERNIST, because it deals only with diseases pertaining to internal medical, the broadest and largest medical specialty. The system is still being completed and refined, but the researchers hope to have it in the working clinical environment within five years.

The two Pittsburgh researchers, Dr. Jack Myers, a physician, and Dr. Harry Pople, a Ph.D. in the University's Graduate School of Business, have developed their medical diagnostic system with the help of high technology equipment funded by the Biotechnology Resources Program of NIH's Division of Research Resources. The Biotechnology Resources Program conceives, develops, and assures the availability of resources that apply the physical sciences, mathematics, and engineering to biology and medicine.

According to Drs. Myers and Pople, the knowledge base underlying INTERNIST is based on two types of information--disease entities and disease manifestations.

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The system includes approximately 350 diseases and 2,800 manifestations.

"Each disease entity has an associated list of manifestations known to occur in that disease recorded, along with an estimate on a scale of one to five of the frequency of occurrence," Dr. Myers says. "The inverse of this relation also is recorded explicitly in the knowledge base; thus, each manifestation is associated with a list of diseases in which the manifestation is known to occur with a weighing factor on a zero to five scale intended to reflect the strength of the association."

According to the professors, the system uses a hierarchy of disease categories, organized primarily around the concept of organ systems. Categories at the top level include diseases such as "heart disease," "lung disease," and "liver disease." Each of these areas is divided into more specific categories, which may be further divided until they reach the final level made up of specific disease entities.

The task of INTERNIST is one of problem formulation, not problem solving, according to Dr. Myers. "INTERNIST is really a simulation of the mental processes of a physician in analyzing a complex case," Dr. Pople says. "It generates and tests hypotheses, much as a clinician would formulate a model as a basis for clinical problem solving."

The computer informs the physician what data it is disregarding for the time being and on what it intends to focus. It questions the user about other observations and laboratory tests, with the computer retiring occasionally to briefly reflect on the additional information.

Each time it returns, the computer lets the user know the leading

(more)

COMPUTER (CONT'D)

diagnostic contenders which it is considering. Eventually, it will inform the physician either that the considered disease has been confirmed or that it is now considering a new hypothesis.

"One of the most important things we've taught the machine is to deal with the least costly things first," Dr. Myers says. "That not only means dollars expended for laboratory use by the patient, but cost also defined as physical pain and danger to the patient."

Another benefit of the INTERNIST system is the development of a new medical textbook, according to its developers.

"The system lists under each disease all of the manifestations of the disease together with two bits of mathematical information about each manifestation; ranked from one (rare) to five (essentially always)," Dr. Myers explains.

"Students, house officers, and mature physicians have already found the data to be useful organization of medical knowledge for clinical purposes. The 'textbook' is large even in its incomplete state, but is easy to use once one gets the hang of it. The data when complete and carefully validated will have application not only to the practical diagnosis of complicated and complex clinical problems, but can be used effectively for teaching and testing, and perhaps even for chart review."

Dr. Myers feels that physicians will accept and become comfortable with computers in the near future. "The modern physician will of necessity become more and more involved with the products of computer storage and analysis of data and he must stay abreast of developments in the field," Dr. Myers says. "Some clinicians are wary and distrustful of computers, at times due to unfavor-

(more)

able experience with them, but it must be recognized that computerization of knowledge, when done with good accuracy, provides a means for storage and manipulation of information which the human brain and orthodox written communications cannot equal."

The INTERNIST system utilizes the large SUMEX-AIM computer facility of Stanford University, Stanford, California, another Division of Research Resources-funded project. The SUMEX system has been developed to provide a national shared computer facility for medical research concentrating on the application of artificial intelligence to medicine. The Bureau of Health Manpower also provided funding for the development of INTERNIST.

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COMPUTER (CONT'D)

Drs. Jack Myers (left) and Harry Pople of the University of Pittsburgh discuss video information display resulting from a hypothetical medical problem posed to their INTERNIST computer diagnostic system. INTERNIST, which can help physicians diagnose internal medicine diseases, uses high technology equipment funded for the University of Pittsburgh by NIH's Division of Research Resources. (NIH Photo # 1611)

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ASPIRIN'S ANTI-CLOTTING PROPERTIES--FOR MEN ONLY?

The effectiveness of aspirin's anti-clotting properties seems to be associated with gender. Boston investigators--funded in part by NIH's National Heart, Lung, and Blood Institute--have found that 1.2 grams of aspirin per day (about four tablets) protects against dangerous blood clotting after surgery--in males but not in females.

Blood clot formation in the large inner veins of the legs--also known as deep vein thrombosis--is a frequent complication of certain medical disorders, surgical procedures and trauma; it becomes more frequent with age. Deep vein thrombosis is dangerous because it may lead to pulmonary emboli, that is, blood clots which travel through the venous system and become lodged in the lungs. Pulmonary embolism can be fatal if enough lung tissue is killed from lack of blood supply.

Situations in which deep vein thrombosis and pulmonary embolism may occur are common. For example, 5 million adults had surgery last year. The diagnosis of these thromboembolic disorders is elusive, the treatment is unsatisfactory, and the preventive medications currently available are not suitable for widespread use. About 50,000 people die each year of pulmonary embolism, many of whom might otherwise have survived the original illness or operation.

Blood clot formation is a complex, multistep process involving the blood elements known as platelets. Drugs that alter platelet function, such as aspirin, may provide a means of preventing thromboemboli that is both simple and largely free of dangerous side effects (severe bleeding). Yet, until now, no rigorous tests of aspirin's anti-clotting effects had been performed.

The investigators chose to test aspirin on patients 40 years and over

(more)

undergoing total hip replacement surgery--a group at high risk for thromboembolism. None had a history of thromboembolism, vein operations, or sensitivity to aspirin.

Patients were prohibited from taking aspirin for two weeks before surgery. One group was given 0.6 grams of aspirin--two 5-grain tablets--twice daily beginning the day before the operation and until about three weeks after. The other group took the same amounts of placebo.

Three tests for thromboembolism were used to ensure thorough and accurate diagnosis. Those who interpreted test results had no knowledge of who took aspirin or of other test results. If blood clots were detected the patient was removed from the study and treated. In only one case did pulmonary embolism develop; it was not fatal.

Results showed that only 11 of 44 (25 percent) on aspirin developed thromboembolic disease compared to 23 of 51 (45 percent) on placebo.

Further analysis of the data with respect to gender yielded a surprise: for men, 4 of 23 on aspirin versus 14 of 25 on placebo developed blood clots. But for women, the figures were 7 of 21 versus 9 of 26. The researchers discovered that an earlier study had had similar results: only 3 of 15 men on aspirin developed blood clots compared to 15 of 27 women. They suggest that this sex-linked phenomenon needs further investigation.

This study was reported by William H. Harris of Massachusetts General Hospital and associates in the December 8 issue of the *New England Journal of Medicine*.

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This was prepared by Constance Raab
National Heart, Lung, and Blood Institute

SCIENTISTS SEEK ANIMAL MODEL FOR CYSTIC FIBROSIS

The possibility of the development of a suitable laboratory animal model for the study of the yet unconquered disease, cystic fibrosis (CF), was announced recently at the Yerkes Regional Primate Research Center in Atlanta, Georgia.

Scientists at NIH's Division of Research Resources-supported center have discovered what appears to be CF in a young rhesus monkey at autopsy--the first nonhuman case of this disease known to medical science.

A report on the discovery was made by veterinary pathologists Drs. Joel Wallach and Harold McClure at a primate pathology workshop on March 4, 1978.

The discovery came as Dr. Wallach, assistant pathologist at Yerkes, was performing a routine autopsy on a six-month male rhesus monkey that had died of unknown causes. He noticed pancreatic disease and bronchial mucus production. Evaluation of the tissue under microscope revealed CF-like abnormalities. Studies of tissues from other organs confirmed that the monkey was apparently a victim of CF. The diagnosis was later confirmed by an Emory University pediatric pathologist, and a well known Chicago pathologist who is considered a national authority on CF.

CF is a disease of children, adolescents, and young adults characterized by abnormal mucus secretions and fibrous scarring in various organs, such as the pancreas, liver, lungs, and reproductive and digestive systems. Many of its victims die in early life of complications, such as malabsorption and pneumonia.

More than 25,000 Caucasians in the United States have the disease, but a much larger number are thought to be carriers of the recessive gene of

(more)

MODEL (CONT'D)

cystic fibrosis. It is rarely seen in the black population or people of Asiatic origin.

Since the 1938 medical recognition of CF as an inherited disorder, scientists have searched for an animal which could have the same type of complications found in children and adults as CF. The development of such an animal model could be invaluable in attempting to pinpoint the underlying biomedical defect of CF and in synthesizing drugs and other therapies for CF patients.

Future possibilities for production of additional monkeys with cystic fibrosis are dependent upon identification and breeding of animals which are carriers of the disease.

The scientists at Yerkes are now in the process of constructing a lineage chart in an attempt to trace the ancestry of the affected animal. "We have identified the mother and the father," Dr. McClure said. "They are now living happily together. They, of course, have been examined and really don't show anything. If they're just carriers, they wouldn't. We also have a number of half-siblings--from other fathers--but they're all males."

The infant rhesus monkey was bred in a colony supported by the National Aeronautics and Space Administration for studies pertaining to the space program.

"It was fortunate that this discovery surfaced in a colony where we have kept extensive records for the past ten years," Dr. McClure said. "The infant was born at Yerkes--so were the father and mother--so were the grandparents, and maybe the great grandparents. So, we can go back three or four

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generations in putting together a genetic chart."

Dr. Wallach will participate in a May 25-26 workshop on "Model Systems for the Study of Cystic Fibrosis" at the National Institutes of Health in Bethesda, MD. The workshop is sponsored by NIH's National Institute of Arthritis, Metabolism, and Digestive Diseases and by the Cystic Fibrosis Foundation.

#

NIA DISPUTES MYTHS ABOUT SEXUALITY OF THE ELDERLY

"Men and women do not lose the capacity for sexual fulfillment. The need for sex is basic to all human beings and desexualization is ageism in its most extreme form."

In addition, according to Robert N. Butler, M.D., Director of NIH's National Institute on Aging, elderly people have been victims of a wealth of myths surrounding their sexuality.

Speaking before the American Association of Sex Educators, Counselors, and Therapists on March 31 at the Mayflower Hotel in Washington, D.C., Dr. Butler emphasized that older people display--and are entitled to--an active interest in continuing their sex lives.

Dr. Butler explained that "Psychologically, the sex act offers many older people affirmative evidence that the body is still reliable and functional. It is a means of self-assertion in a society where most traditional means of assertion are denied to older people."

Dr. Butler stressed that sex education should be readily available to the elderly. He told the audience of researchers and counselors in the field of sex education that normal physiological changes accompanying aging must be explained so that neither men nor women regard them as indicative of a loss of sexuality.

Dr. Butler went on to point out that older people themselves often accept society's negative sexual stereotypes. The distorted body images and self-hatred engendered in older people by these attitudes not only impair sexual functioning, but also further discourage sexual activity.

Tests conducted at the National Institute on Aging's Gerontology Research

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MYTHS (CONT'D)

Center in Baltimore, show that men who were sexually active throughout their lives tend to remain so in old age. A study of 188 males aged 60 to 79 has identified some previously-unrecognized factors which appear to influence sexual functioning. Much sexual inactivity of the older male stems from apathy or indifference to stimuli which previously caused erotic reactions. Sexually inactive subjects felt no pressure to perform and the vast majority had never sought help for their condition.

One of the most distressing myths surrounding sex and the elderly is the belief that "sex is bad for your heart." Many heart patients particularly older ones, are afraid that coitus is too strenuous and can provoke a heart attack.

Dr. Butler stressed that studies conducted on male cardiac patients show that they can enjoy coital activities several weeks after a heart attack (after moderate physical activities have been resumed). A cardiac patient should check with his doctor before resuming sexual activities.

#

CONFERENCE STUDIES DIARRHEAL DISEASES FOUND IN THE YOUNG

Diarrheal diseases of the young are caused by similar pathogens whether "the young" are calves, piglets, or human babies. A conference to exchange information about these organisms and the diseases they cause was held in March at the National Institutes of Health.

Participants included physicians, veterinarians, microbiologists, and pathologists from the United States and three foreign countries who have an active interest in the clinical and research aspects of diarrheal diseases.

Dr. Milo D. Leavitt, Director of the Fogarty International Center, and Dr. Kenneth E. Sell, scientific director of the National Institute of Allergy and Infectious Diseases, welcomed the participants. They noted the contributions of veterinarians in discovering and defining the role of various pathogens in diarrheal diseases of animals, providing a groundwork for similar studies in human beings.

NIAID intramural scientists, in particular, have been working closely with veterinarians in State and Federal agricultural organizations studying diarrhea in calves and piglets.

One widespread cause of diarrhea in human infants and other young animals is the rotavirus. Scientists have already developed for calves a vaccine licensed by the USDA.

Lambs have been experimentally protected by feeding serum and colostrum-derived anti-body--an example of passive, short-term immunity. The possibility of protecting human infants and young children can be explored using knowledge gained from these experiences with animals.

Other common causes of diarrhea include parvoviruses (cat distemper),

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corona viruses, and a variety of bacteria including toxigenic and invasive *E. coli*, *Salmonella*, and *Cryptoposidia*.

The participants agreed that neonates succumb to diarrheal diseases, not because of the viral or bacterial agent, but more often because of the loss of electrolytes and water with consequential dehydration, acidosis, and shock.

Therefore, any program developed to control diarrheal diseases must emphasize preventive measures and supportive treatment.

This was one of a series of conferences sponsored by the American Veterinary Medical Association and was jointly sponsored by FIC; NIAID; the Bureau of Biologics, FDA; Animal Research Service, and Animal and Plant Health Inspection Service, USDA; and several commercial companies.

#

NEW TRIAL SET FOR TREATMENT OF DIABETIC RETINOPATHY

A new nationwide clinical trial of early treatment for diabetic retinopathy, a leading cause of blindness in the United States, was announced in March by NIH's National Eye Institute (NEI).

The study, involving 21 research centers, will examine the use of laser treatment and drug therapy for the disease, a common eye complication of diabetes.

Diabetic retinopathy is a progressive disease which causes harmful changes in the blood vessels of the retina--the light sensitive tissue at the back of the eye.

In the more severe or proliferative stage of diabetic retinopathy, the retina may detach from underlying tissue layers. A detached retina is not able to generate and transmit nerve impulses to the brain properly; so, vision is reduced or lost.

Data from a previous NEI-supported trial showed that laser treatment can reduce the risk of blindness in patients in advanced stages of this disease. In that study, however, some patients' eyes became blind in spite of treatment, and in some, harmful side effects of treatment were noted, such as mild blurring of vision and narrowing of side vision. The new study seeks to determine whether treatment at an earlier stage of retinopathy may be of greater value in reducing the risk of blindness and, if so, whether this benefit outweighs the risk of adverse side effects.

Investigators in the study also hope to find out whether laser treatment may be effective against macular edema, an abnormal accumulation of fluid in the retina. It frequently accompanies diabetic retinopathy and may cause

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RETINOPATHY (CONT'D)

blurred central vision.

A third objective of the study is to determine whether aspirin, either alone or in combination with another drug, may be useful in treating diabetic retinopathy. In diabetics, there is an increased tendency for blood platelets to clump. This may affect the flow of blood through small vessels, such as those present in the retina, and contribute to the development of retinopathy. Because aspirin interferes with clumping of blood platelets, it may be effective in preventing blockage of the retinal vessels in diabetic retinopathy.

Patient enrollment in the new study will begin following a planning stage of about one year. Eventually, 3,000 patients are expected to participate. It is expected that each will be followed for five years to provide long-term information on the risks and benefits of both kinds of treatment being examined. The average cost of the projected seven to eight year study is an estimated $3 million per year. The HEW Center for Disease Control in Atlanta, Georgia, plans to provide - through an interagency agreement - a central laboratory for the study to monitor drug treatment of patients.

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REPORT STRESSES PROTECTION OF THE MENTALLY INFIRM

HEW Secretary Joseph A. Califano, Jr., announced on April 17, 1978, the publication of the report and recommendations on "Research with Those Institutionalized as Mentally Infirm" transmitted to him by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research.

Published in the Federal Register on March 17, the report stressed the need to protect the institutionalized mentally infirm as vulnerable persons, and to protect their right to make decisions for themselves to the extent they are able to do so. The Commission noted that the medical, psychological, and social protection of mentally infirm people depends upon society's knowledge of their disabilities and their treatment and care. This knowledge is critically dependent upon research, the Commission said.

The Commission recommended that institutionalized mentally infirm persons not be asked to participate in research unless it has first been established that the research will not interfere with their care. The Commission also recommended that mentally infirm persons who are not capable of giving consent on their own behalf must not be involved in research unless the research is relevant to their own condition. Finally, no mentally infirm persons should be involved in research over their objection unless the research is intended to directly benefit them or is specifically authorized by a court.

In addition, the Commission recommended that review boards located at institutions conducting research with the mentally infirm be required to establish the safety of all such research, the competence of the researcher, and the adequacy of the procedures to protect patient privacy.

Under no circumstances is any minimal risk research to be carried out

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PROTECTION (CONT'D)

without the consent of the patient or, if the patient is not legally competent to consent, the assent of the patient and the consent of a legal guardian, the Commission said. If the patient is legally incompetent and refuses to assent to involvement in research considered to be potentially beneficial, the institution may seek authorization of a court of competent jurisdiction.

The Commission would also require that doctors show that there would be benefits to the subject if the risks of the research were appreciably above the minimum. Actual performance of any such research would require approval of a national ethical advisory board and the Secretary of HEW, in addition to institutional review board approval.

The Secretary has six months after publication to review the Commission's recommendations and decide whether or not to propose regulations with respect to them.

Copies of the report are available from the Office for Protection from Research Risks, National Institutes of Health, Bethesda, Maryland 20014, (301) 496-7005.

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NEWS & FEATURES From NIH
May 1978

NON-A, NON-B HEPATITIS IS UNDER STUDY AT NIH, FDA

Two teams of Federal scientists have demonstrated for the first time that a transmissible agent which can remain infectious over prolonged periods is responsible for non-A, non-B (post-transfusion) hepatitis.

This form of hepatitis only recently has been identified as a disease entity separate from the well known viral forms of hepatitis, type A (infectious), and type B (serum). The clinical and microscopic similarities of non-A, non-B hepatitis to the previously recognized forms and the new evidence of its transmissibility points strongly to a viral cause.

In independent studies headed by Dr. Harvey J. Alter of NIH's Clinical Center and Dr. Edward Tabor of the Food and Drug Administration's Bureau of Biologics, chimpanzees innoculated with plasma or serum from patients with either acute or chronic non-A, non-B hepatitis developed biochemical and biopsy evidence of the disease. The investigators reported in the March 4, 1978, issue of *Lancet* that the ability to transmit hepatitis using chronic phase plasma indicates that there is a chronic asymptomatic carrier state for non-A, non-B hepatitis, just as there is for type B hepatitis.

The development in the early 1970's of sensitive immunologic tests to detect the hepatitis B surface (Australia) antigen has enabled scientists to identify most of the blood donors carrying the hepatitis B virus. The application of these tests and the exclusion of commercial donors has led to a dramatic reduction in the incidence of post-transfusion hepatitis. However, contrary to physicians' hopes and expectations, some post-transfusion hepatitis continued to appear. Presently 70 to 90 percent of post-transfusion hepatitis is serologically unrelated to either the type A or B viral agents and is

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tentatively classified as non-A, non-B.

The studies by Drs. Alter, Tabor, and their co-workers provide the first direct evidence that non-A, non-B hepatitis is caused by an infectious agent.

The availability of an animal model will now allow for a more definitive characterization of the non-A, non-B agent, including its infectivity and whether more than one variety of non-A, non-B hepatitis exists. It is hoped that these studies will lead to the visualization of virus material in liver tissue, to the development of a serologic test for non-A, non-B hepatitis, and ultimately, to the elimination of post-transfusion hepatitis.

Working with Dr. Alter were Dr. Robert H. Purcell, National Institute of Allergy and Infectious Diseases, Dr. Paul Holland, NIH Clinical Center, and Dr. Hans Popper, Mount Sinai School of Medicine of the City University of New York. Dr. Tabor's associates include Dr. Robert J. Gerety, Dr. Lewellys F. Barker, Dr. Jacques A. Drucker, Mr. Daniel R. Jackson, and Dr. Milton April, all of the Bureau of Biologics, FDA; Dr. Leonard B. Seeff and Dr. Jay H. Hoofnagle, Veterans Administration Hospital, Washington, D.C.; and, Dr. G. Pineda-Tamondong, American Red Cross.

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NEWS & FEATURES From NIH

May 1978

NIAMDD PUBLISHES BOOKLET CALLED "DIABETES DATA"

NIH's National Institute of Arthritis, Metabolism, and Digestive Diseases (NIAMDD), has announced the issuance of a new publication, *Diabetes Data,* a compilation of statistical information relevant to the full scope of this public health problem.

Diabetes, a derangement of carbohydrate and lipid metabolism, is known to affect a population of about 4.8 million Americans. It has been estimated, however, that an equal number of individuals will develop, or have undetected, diabetes. In 1977, this disorder cost the nation approximately $6 billion in lost productivity and medical expenses -- an average of $1,124 per patient -- even without considering the cost of complications.

Coupled with the escalating economic loss from diabetes is the inestimable toll taken from the quality of life of affected individuals. Diabetes ranks fifth as a cause of death by disease and is a major factor in the development of cardiovascular, ocular, renal and neurologic complications in the diabetic population.

Because of the broad scope and impact of this public health problem, the need for accurate demographic and epidemiologic data on diabetes has become essential. In response to this need, NIAMDD's National Diabetes Data Group has published *Diabetes Data,* a compilation of facts ranging from clinical information to the socioeconomic impact of the disease. Prevalence and incidence data, morbidity of long-and short-term complications, and diabetes mortality complete the statistical scope of the publication.

Three major factors provided the impetus for the compilation of *Diabetes Data:* the development of new information and concepts of diabetes over the

(more)

BOOKLET (CONT'D)

past decade; the extensive updating, assembly, and discussion of data by the National Commission on Diabetes; and the need for a current collection of diabetes statistics for program planning by health agencies. The new publication provides a central source of this information for clinicians and allied health professionals, scientific investigators, service program coordinators, and for all who are concerned with the public health aspects of diabetes.

Diabetes Data was prepared by the National Commission on Diabetes in collaboration with the NIAMDD, the National Center for Health Statistics and the American Diabetes Association. The NIAMDD is the focal point for the Federal Government's research programs on diabetes.

The National Diabetes Data Group, established within the Institute's Diabetes, Endocrine and Metabolic Diseases Program, directed the publication of *Diabetes Data*. In accordance with the Commission's recommendation, the Data Group was instituted in recognition of the need for a systematic approach to the design, collection, analysis, documentation and dissemination of data to support a public health policy on diabetes and to provide a basis for evaluating the Commission's Long-Range Plan to Combat Diabetes. *Diabetes Data* is the group's initial effort to present current statistical information in this important disease area.

Single copies of *Diabetes Data* are available free of charge from the National Institute of Arthritis, Metabolism, and Digestive Diseases, Building 31, Room 9A-04, Bethesda, Maryland 20014; or the publication may be purchased in quantities from the Superintendent of Documents, Government Printing Office, Washington, D.C. 20402; DHEW Publication No. (NIH) 78-1468.

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MEDICINE IN EARLY WEST IS NLM EXHIBIT THEME

NIH's National Library of Medicine (NLM) has opened a new exhibit "Medicine on the Early Western Frontier." It will be on view in the main lobby of the Library (located at 8600 Rockville Pike in Bethesda) through September 15.

The exhibit focuses on health and medicine as experienced and practiced in the trans-Mississippi West by early Anglo-American explorers, by the fur trappers, by the military in isolated posts along the expanding frontier, by the emigrants along the overland trails, and finally by the early settlers.

The exhibit features published and unpublished materials (including diaries of early military surgeons on the frontier, from the NLM collections); pictures of the early West from the Western History Collection, Denver Public Library, and other sources and artifacts. Among the artifacts will be a skull of a man killed near Fort Concho, Texas, in 1868; early surgical instruments, including arrow-extracting forceps developed in 1876; a medicine case from the Spanish southwest; and the fur trappers' "Green River" knives used as bleeding instruments as well as for amputations. Also exhibited will be examples of the firearms so frequently used by the frontier citizenry.

The exhibit may be viewed weekdays from 8:30 a.m. to 9 p.m. and Saturdays from 8:30 to 5. Summer hours (8:30 to 5, Monday through Saturday) go into effect May 30. The Library is closed on Sundays and on May 27, May 29, July 4, September 2, and September 4. Tours of the Library, lasting about an hour, are given daily at 1 p.m. No advance reservations are necessary.

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Editors of publications may request a glossy print of the numbered photographs that appear in this issue.

Mrs. Joyce F. McCarthy
National Institutes of Health
Building 31, Rm. 2B-10
Bethesda, Maryland

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NEWS&FEATURES FROM NIH

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE■Public Health Service■National Institutes of Health■Office of Information■Bethesda, Maryland 20014

AUG 28 1978

NATIONAL INSTITUTES OF HEALTH

August 1978

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NITROGLYCERIN MAY LOWER BLOOD PRESSURE DURING SURGERY

By JULIE KLUG

Nitroglycerin (TNG) has been effectively utilized as a hypotensive drug during general anesthesia, and may prove to be superior to drugs currently used for lowering blood pressure during surgery. Hypotension, or lowered blood pressure, is desired during anesthesia for several reasons--the surgical field is relatively bloodless, operative blood loss is diminished, and both the need for and risks of blood transfusion are reduced.

Currently available agents, such as ganglionic-blocking drugs and sodium nitroprusside (SNP), may produce adverse effects including tachyphylaxis (tolerance to drug action, which increases the dosage required to maintain the desired action), cyanide poisoning, and even death. However, in this study, supported in part by NIH's National Institute of General Medical Sciences, the use of nitroglycerin during general anesthesia for major orthopedic surgery brought about no undesirable side effects.

Dr. Nabil R. Fahmy, Assistant Professor in Anesthesia, Harvard Medical School, evaluated the effects of nitroglycerin administered intravenously to 91 patients scheduled for total hip replacement. Since TNG currently is used to reduce blood pressure in patients with heart failure or after acute myocardial infraction (heart attack), as well as to control hypertension (high blood pressure) during coronary artery surgery, Dr. Fahmy chose to further assess its use in surgery.

The patients studied ranged in age from 18 to 72 years (average 46 years), and none showed any history or evidence of cardiovascular, pulmonary, or metabolic disease. The subjects were divided into two groups similar with regard to age, sex distribution, and weight--44 patients received TNG and

(more)

47 were administered SNP, which is currently in widespread usage.

Both groups of patients received the same premedication and were anesthetized with a standard technique. Prior to the actual surgery, arterial hypotension was obtained in all subjects by continuous intravenous administration of either TNG or SNP. When infusion of the drugs was halted, arterial pressure was permitted to return to original levels before wound closure in order to insure checking of the flow of blood.

For all patients, circulatory and blood-gas values were measured prior to anesthesia administration, after administration but before induction of hypotension (control value), at 15-minute intervals for a total of 90 minutes during hypotension, and after blood pressure returned to within 10 percent of the control value.

Several important differences were noted between the effects of the two drugs. Some patients who received SNP required increased doses of the agent in order to maintain hypotension. However, there was no evidence of such tachyphylaxis occurring in the group who received TNG. In addition, with the administration of SNP, significant increases in heart rate (as compared to pre-drug measurements) were noted at 15, 30, 45, and 60 minutes. With the use of TNG, a significant rise in heart rate occurred only after 15 minutes; further deviations were not significant.

The intraoperative blood loss in the SNP group was approximately 184 ml greater than the group given TNG. In addition, 18 of the 47 patients who received SNP exhibited temporarily altered electrocardiograms, while those

(more)

NITROGLYCERIN (CONT'D)

receiving TNG showed no evidence of change.

During the postoperative periods, no clinical evidence of myocardial infarction, kidney damage, or vascular brain complications was seen in either group.

Nitroglycerin has been shown to increase coronary blood flow in both animals and man. Under the influence of TNG, the blood vessels of the heart become dilated, lowering the coronary blood pressure. Because of these effects, TNG decreases the chances of heart muscle injury due to ischemia (inadequate blood supply). SNP, however, decreases myocardial blood flow, increasing the risk of ischemia of heart tissue.

This investigation indicates that nitroglycerin is an efficacious hypotensive drug useful during general surgery. TNG is easy to administer and elicits rapid patient response. The blood pressure is reduced gradually and smoothly, minimizing the danger of inducing severe low blood pressure. TNG, unlike SNP, provides sufficient coronary blood flow, guarding the heart muscle from injury due to inadequate blood flow. There were no side effects, such as tachyphylaxis, attributable to TNG administration in this study. The successful application of TNG in the described surgical situation indicates the utility of further trials in other situations where deliberate hypotension during anesthesia is desired.

These findings were reported in the July 1978 isssue of *Anesthesiology*.

#

Julie Klug, an NIH Summer Information Aide, is
a senior at The Ohio State University, Columbus.

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CONJUGATED ESTROGEN TABLET IS TESTED AS CONTRACEPTIVE

A conjugated estrogen tablet (one made of a mixture of estrogens obtained exclusively from natural sources) was tested and found to be effective in preventing pregnancy after unprotected, mid-cycle sexual intercourse. It was as effective in preventing pregnancy as other commonly used "morning after" pills containing diethylstilbesterol (DES) or ethinyl estradiol, but was associated with fewer and milder side effects.

In a study supported by NIH's National Institute of Child Health and Human Development at the University of Florida, the drug was administered to 359 young women who had intercourse near the expected time of ovulation without using a contraceptive. Only one pregnancy resulted -- a failure rate of 0.3 percent.

Most of the patients in the study reported some side effects but generally the degree of discomfort was mild. The most common side effects were nausea (52.3 percent) and breast tenderness (37 percent). The character and bleeding pattern of the menstrual cycle was unaffected in 69.3 percent of the women.

The conjugated estrogen product used in this study was Premarin^{TM}. This drug is currently used as replacement therapy for naturally occurring or surgically induced estrogen deficiency, for some types of abnormal uterine bleeding, and for prevention of postpartum breast engrogement.

Women in the study were given 10 mg. of Premarin^{TM} three times a day for five consecutive days following a negative pregnancy test. Therapy was started within 72 hours of intercourse. The patients were interviewed one week after the start of treatment to determine whether the drug had been taken as directed, the occurrence of side effects, and the patient's future contraceptive needs.

(more)

CONTRACEPTIVE (CONT'D)

Six weeks later each patient was re-examined. This included a repeat pregnancy test and a full general, pelvic, and breast examination. Of the 377 women accepted into the study, only 18 failed to complete the six week therapy and follow-up program. Of these, only two were completely lost to follow-up. Of the remaining sixteen, some had menstruated before their scheduled visit and did not return as requested, and others did not take the medication as directed. All were contacted, however, and none were found to be pregnant.

Women were not accepted into the study if they had a history of neoplasia of the breast, reproductive tract or pituitary gland; hypertension; migraine headaches; seizures, phlebitis; hepatitis; or cardiac disease.

The study was conducted from July 1973 to July 1977.

It was reported in the May issue of *Contraception* by Dr. Morris Notelovitz of the University of Florida at Gainesville and Dr. David Sayre Bard of the University of Tennessee in Memphis.

#

NIEHS "GRIP TEST" MEASURES CHEMICAL EFFECTS ON SMALL ANIMALS

Scientists at NIH's National Institute of Environmental Health Sciences (NIEHS), have developed an ingenious and low-cost unit that precisely measures the grip strength of lab animals. Used in studying the effects of different environmental chemicals on nerve and muscle systems, gauging grip strength is of great importance in environmental health research.

The innovation was recently published in the professional journal of *Pharmacology, Biochemistry & Behavior*. Referred to as a Simple Recording Grip Strength Device, it was developed by Drs. Patrick A. Cabe, H.A. Tilson and Clifford L. Mitchell in the Laboratory of Behavioral and Neurological Toxicology, NIEHS. They were assisted by machinist Ralph Dennis in the Research Services Branch also at NIEHS.

The device is made from a lightweight strain gauge which is equipped with a grasping ring and mounted on a stand parallel to a lab table. A hand-held animal is lowered close to the ring which it grasps by reflex. It is then pulled gently away from the strain gauge until it lets go of the ring. The gauge records the maximum pull in grams required to release the animal's grip.

The test which requires no learning behavior from the animal is repeated three times to obtain an average result. The method was first tried using animals that had been administered chemicals that had a known effect on muscle and nerve systems.

"An advantage to this device is that it measures increased grip strength as well as decreased strength," Dr. Mitchell said. Also, he noted the device provides a quantitative result. "Previous methods provided all or nothing

(more)

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STRENGTH (CONT'D)

results," he said.

Already the device has been used in a number of projects, for example, research on the polybrominated biphenyls (PBBs).

PBBs came to light as an environmental problem in Michigan in 1973 where a chemical fire retardant used in solid plastics was bagged and used mistakenly as an additive for cattle feed. Disease symptoms were later reported in the cattle that ate the feed and in people who ate animal products from the cattle.

Human symptoms reported by those exposed to PBBs include sores, loss of hair, loss of memory, and fatigue, among other problems.

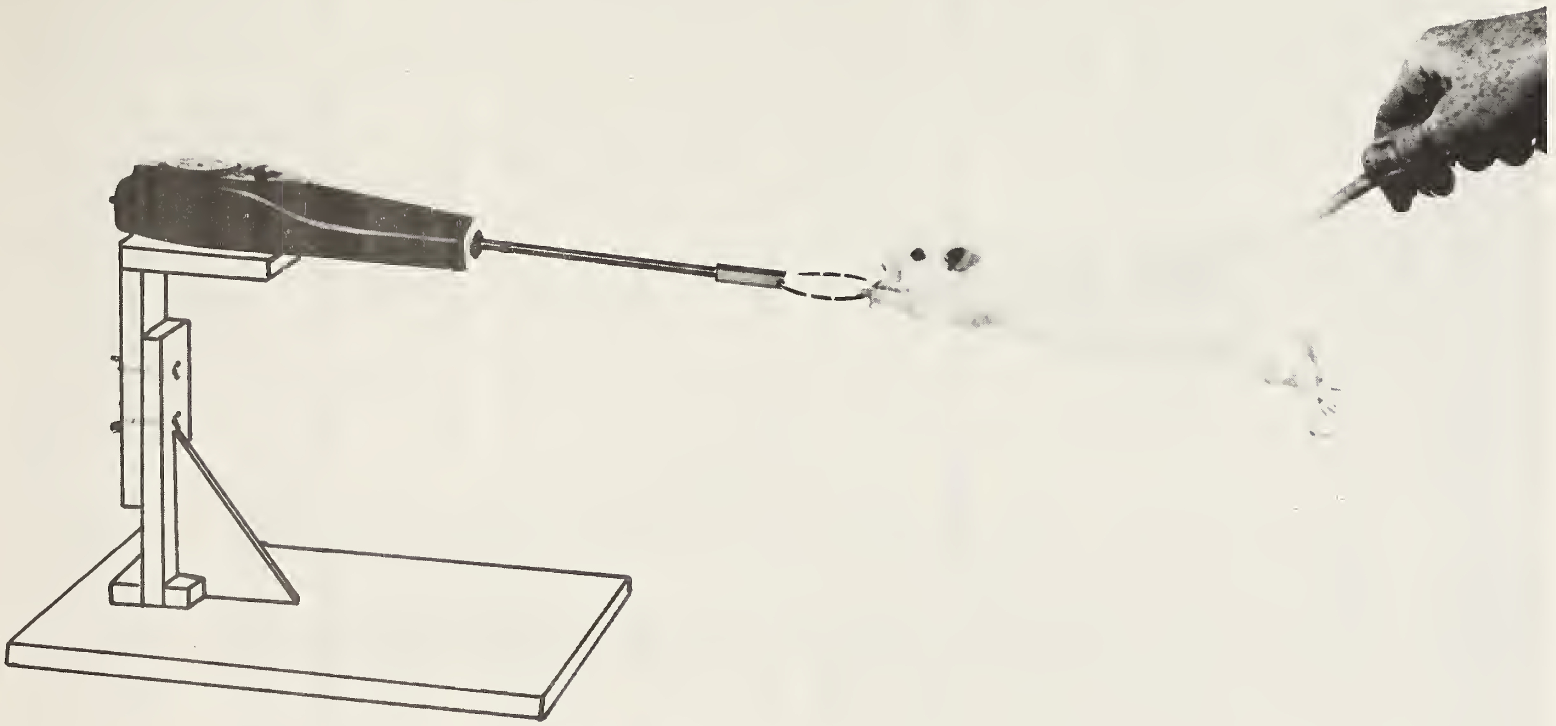
This experience recalled a similar contamination of rice oil in Japan in the 1960's which involved a related chemical product, polychlorinated biphenyls (PCBs).

Research was done at NIEHS and by scientists at the NIEHS-supported Environmental Health Sciences Center at the Mt. Sinai School of Medicine in New York City to determine the effects of PBBs and PCBs. The grip strength device was developed at NIEHS to determine what effects these chemicals had on the nerve and muscle systems of lab animals.

This research can provide crucial information to the regulatory agencies for their use in determining guidelines for the manufacture and distribution of these and other chemical products.

(more)

STRENGTH (CONT'D)



As a researcher lowers the rat, by reflex it grasps the ring. It it then pulled gently away from the strain gauge until it lets go of the ring. The maximum pull in grams required to release the animal's grip is recorded by the gauge. (NIH Photo #1612)

#

PUBLIC HEARING ON REVISED DNA GUIDELINES IS SEPT. 15

The National Institutes of Health has proposed revised guidelines to control NIH-funded research on recombinant DNA, HEW Secretary Joseph A. Califano, Jr., has announced.

The proposed revision appeared in the *Federal Register* of Friday, July 28, 1978.

"I recognize the extraordinarily difficult challenge that sensitive but effective regulation in this field poses for NIH, for the research community, and for the concerned public," Secretary Califano said.

The Secretary indicated that before the revised guidelines become effective, he would have all public comments reviewed by a high level Department committee, which would also hold a public hearing on the issue September 15, in the Washington, D.C. area. The final revised guidelines will be issued promptly following the hearing and the end of the comment period.

Deoxyribonucleic acid, known as DNA, is the material which determines the hereditary characteristics of all living cells. Recombinant DNA molecules contain segments of DNA from unrelated organisms which have been combined in the test tube. Genetic recombination itself, other than what is referred to as recombinant DNA, occurs in nature.

The research techniques used to produce recombinant DNA molecules have a remarkable potential for furthering the understanding of fundamental biochemical processes in cells of lower and higher organisms, and promise to revolutionize molecular biology.

As proposed, the NIH guidelines would exempt five classes of recombinant DNA experiments now known to be safe, provide a way to remove others upon

(more)

GUIDELINES (CONT'D)

proof of their safety, and place primary responsibility for assuring compliance on institutions where the research is done. The present ban would continue, however, on recombinant DNA research now considered high risk, and institutions would still be required to seek NIH approval before initiating projects or changing the conditions of certain experiments.

Also, for the first time, provisions will be made for private industry to register its recombinant DNA activities with NIH.

Dr. Donald S. Fredrickson, NIH Director, observed:

"Five years have passed since concerns were first raised about the hypothetical hazards of laboratory experiments with recombinant DNA. Thousands of these experiments have produced much useful knowledge, but no evidence has come to light of a product created by these techniques that has been harmful to man or the environment."

The NIH guidelines, he emphasized, are being revised to keep up with new knowledge in this highly active field and not in preparation for their early abandonment. "We are searching for any risks and will propose additional standards as needed," he said.

The NIH guidelines were first issued on June 23, 1976, as a result of the concerns expressed within the scientific community regarding possible dangers from recombinant DNA research. The proposed revisions result from scientific experience with such research and extensive discussions at numerous forums and several Congressional hearings. The NIH Director, on the basis of scientific and technical advice and of a public hearing held in December 1977, concluded that there was widespread agreement on the need

(more)

to update the original guidelines. He noted that the NIH has received numerous suggestions for their revisions.

The standards of the guidelines would apply to all recombinant DNA experiments, however supported, that are conducted in an institution receiving any support from NIH for recombinant DNA research. All such experiments must be registered with NIH, even though not all are paid for by the Federal research agency. A research institution would risk losing its NIH recombinant DNA research funds if a non-NIH funded project is not in compliance with the guideline standards.

Prior NIH clearance is mandatory for new NIH grants and contracts involving recombinant DNA techniques and for all projects in P4 facilities. In the proposed revised guidelines, prior NIH clearance is no longer required for changes in ongoing experiments at the P1-P3 levels. These changes must be approved by the institutional biosafety committee (IBC), and NIH will then review the IBC actions.

NIH issued a Draft Environmental Impact Statement on the original guidelines in September 1976. The final EIS, issued that fall, concluded that activities conducted under the guidelines would have no predictable impact on the environment.

In the process of preparing this revision of the NIH guidelines, NIH made an environmental impact assessment which indicates that there would be no impact on the environment as a result of the revisions. The assessment and a lengthy "Decision" statement explaining the proposed revisions also appear in the *Federal Register*.

(more)

GUIDELINES (CONT'D)

Comments and inquiries concerning the proposed revision of the guidelines are invited until late September. All correspondence should be addressed to the Director, NIH, Building 1, Room 124, 9000 Rockville Pike, Bethesda, Maryland 20014.

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NAT'L. CONF. ON HEALTH RESEARCH PRINCIPLES TO BE AT NIH, OCT. 3-4

A National Conference on Health Research Principles will be held at the National Institutes of Health on October 3 and 4, 1978.

The Federal government supports the largest health research establishment in the world today. Last July, President Carter ordered a comprehensive review of Federal support for basic research. Based on this review, the President directed that a new emphasis be placed on research in Federally-supported science programs.

As a speech before the Annual Meeting of the American Federation for Clinical Research held in April 1978, Secretary Califano proposed a new, open process using public advice to develop a multi-year strategy to guide HEW health research activities within the limited funding available.

Approximately 1,000 professional societies and health organizations are being canvassed for their ideas and suggestions.

The Secretary has appointed a Departmental Steering Committee chaired by Dr. Donald S. Fredrickson, Director of the National Institutes of Health, to oversee this process. HEW agencies and organizations that engage in health research activities are now developing draft principles.

The comments received from the health community, the public, and other Federal agencies will be considered in formulating a statement of proposed HEW health research principles to be presented to the National Conference. The results of the Conference will be published to solicit additional public comment.

#

MEET "MUGS," A NEWBORN BABOON, LIVING IN OREGON

Mugs, an infant baboon recently born at NIH's Oregon Regional Primate Research Center in Beaverton, gazes at life somewhat complacently. The infant, as a fetus, and its mother were the first baboons at the Division of Research Resources-supported Center to have indwelling vascular catheters during the prenatal stage. The process was accomplished by Drs. Miles J. Novy and Scott W. Walsh who plan to extend their perinatal physiology research in the rhesus monkey to the baboon. (NIH Photo #1613)

#

NTRACELLULAR PARASITE SHOWN O BE A CAUSE OF PNEUMONIA

The organism *Chlamydia trachomatis* caused 30 percent of all pneumonias in infants hospitalized during a five and one-half month study at the Children's Orthopedic Hospital and Medical Center in Seattle, Washington. This high prevalence suggests that *C. trachomatis* may be responsible for many pneumonias previously considered to be caused by viruses.

C. trachomatis is an intracellular parasite, probably related to bacteria, that causes an eye infection called trachoma; it is also responsible for 0 to 50 percent of cases of nongonococcal urethritis (NGU) in men. Transmitted by sexual contact, the organism also causes inflammation of the cervix in women, which is often asymptomatic. The infection in women may not be suspected until they deliver babies with a chlamydial-caused eye infection. These eye infections are usually benign and self-limited. However, a recent study indicates that these eye infections may precede pneumonia and that the incidence of chlamydial-caused pneumonia is much greater than previously recognized.

Investigators, supported by grants from NIH's National Institute of llergy and Infectious Diseases, examined 30 infants with pneumonia admitted onsecutively to the hospital. Nine of these infants showed evidence of . *trachomatis* infection either by culture of the organisms present in onjunctival and nasopharyngeal secretions or by high or rising levels of nti-chlamydial antibody measured in tear, serum, and nasopharyngeal samples. esults of measuring antibody levels in tears suggested a high incidence of pparent and inapparent conjunctivitis before pneumonia developed. These esults were compared to those from 28 infants without pneumonia who served

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as matched controls. Only one of these 28 infants was positive for *C. trachomatis,* and he did have upper respiratory congestion.

Several distinguishing clinical and laboratory features were noted in infants with *C. trachomatis* pneumonia. All these patients were between three to eleven weeks old, and had had coughs and congestion for one week or longer. The physicians heard abnormal sounds when they listened to the infants' chests, and areas of overinflation were indicated on the chest X-rays. The number of eosinophils, a type of white blood cell, and antibody levels were also significantly higher in these patients. Identification of these features is important since many laboratories are not equipped to culture *C. trachomatis* or to measure anti-chlamydial antibody titers.

Awareness of the prevalence of this infection should aid physicians in making decisions about treatment. Often, infants with pneumonia are treated for bacterial infection with penicillin or ampicillin, drugs ineffective against chlamydial infections. Infants who do not respond to treatment are assumed to have a viral infection against which there is currently no effective treatment. However, infants with chlamydial pneumonia will respond to treatment with erythromycin or sulfonamides.

The investigators acknowledged that the period of the study (September 1, 1977, through February 15, 1978) precisely bisected the respiratory disease season. If the study had been longer, more patients with pneumonia due to respiratory syncytial virus, the most important cause of serious lower respiratory tract illness in children under five, probably would have been seen. The authors feel larger case-control studies and longer follow-up

(more)

PNEUMONIA (CONT'D)

periods are warranted.

This study was reported by H. Robert Harrison, Marilyn G. English, Cynthia K. Lee, and E. Russell Alexander, all from the School of Public Health and Community Medicine, University of Washington, Seattle, in the *New England Journal of Medicine*.

#

DES TASK FORCE IS CONCERNED ABOUT POSSIBLE RISK TO MOTHERS

Although a statistically significant relationship between the use of DES (diethylstilbestrol) during pregnancy and the risk of cancer in mothers has not been established, the DES Task Force has serious concern about the carcinogenic potential of DES in these mothers.

In its first report sent to Dr. Julius Richmond, HEW Assistant Secretary for Health, on May 30, the Task Force recommended that its concern be transmitted through professional and public media to reach all physicians and women exposed to DES during pregnancy.

Physicians should be encouraged to inform their patients of previous DES exposure and to inquire about such exposure when taking medical histories. Women aware of such exposure should notify their physicians.

The Task Force is headed by Dr. Diane J. Fink, director of NIH's National Cancer Institute's Division of Cancer Control and Rehabilitation.

The report covers only one aspect of the DES issue--the question of whether mothers exposed to DES or similar drugs during their pregnancies are at higher-than-average risk of developing breast or other hormone-related cancers.

Dr. Robert Hoover, head of the NCI Environmental Studies Section, was the chairperson of this part of the Task Force assignment.

Symptom-free DES mothers should be urged to have the regular medical examinations considered appropriate for all women over 18.

These include monthly breast self-examination, an annual Pap test and pelvic examination with bimanual palpation, and a physical examination of the breasts by qualified medical personnel. Mammography should be considered only as recommended by NCI guidelines.

(more)

DES (CONT'D)

These recommendations are:

No mammography for women under 35; annual mammography for women between 35-39 only if they have a personal history of breast cancer, and for women 40-49 with a personal history of breast cancer or with a history of breast cancer in immediate relatives.

For women over 50 annual mammography may be considered without these specific qualifications.

Mothers exposed to DES-type drugs are advised to keep to a minimum their exposures to other preparations which include estrogens.

In addition to its use as a "morning after" pill, DES is used for lactation suppression. Other estrogens are used in oral contraceptives or sometimes prescribed for certain menopausal or postmenopausal conditions.

The Task Force recommended that additional studies with DES-exposed mothers be undertaken on a collaborative basis with central coordination and analysis.

In addition, the group recommended that increased emphasis should be placed on appropriate evaluation of the influence of other exogenous estrogen hormones on the risk of cancer, because it is not known whether any risk that might be associated with DES is specific for that drug or associated with estrogens as a class.

Future prospective randomized studies on breast cancer screening as well as studies of cancers of reproductive organs should compare populations of women exposed to estrogens and those not so exposed, the report stated.

The final report of the Task Force, which was appointed in March, will

(more)

DES (CONT'D)

be submitted this summer and will concern the cancer risks and other problems of DES-exposed daughters, sons, and mothers.

Additional research requirements will be indicated and action recommendations made for followup and notification of exposed individuals, health professionals, and the public.

#

August 1978

INTERFERON LIMITS HERPES ZOSTER IN CANCER PATIENTS

Interferon effectively limits dissemination of herpes zoster (shingles) in cancer patients, according to a study by scientists at Stanford University. Treatment with interferon also significantly diminished visceral (internal) complications, such as involvement of the brain, lung, or eyes, as well as the severity of post-herpetic neuralgia in these patients.

Interferon is a natural body protein produced by cells in response to a virus or other stimuli. It can be manufactured in limited quantities in the laboratory by stimulating human white blood cells (leukocytes) or human fibroblast cells with Sendai virus or other interferon inducers. The resulting exogenous human interferon, primarily leukocyte, has been tried with promising results in the treatment of respiratory infections, herpes keratitis, and chronic hepatitis B.

The new study, conducted by Dr. Thomas C. Merigan and his colleagues, was supported by a contract and grants from NIH's National Institute of Allergy and Infectious Diseases (NIAID) and a grant from NIH's National Cancer Institute (NCI). The effect of interferon on early localized herpes zoster infections was tested in a series of three placebo-controlled, randomized double-blind trials involving 90 patients with malignancy. In these patients, herpes zoster can be both serious and prolonged.

The investigators used human leukocyte interferon prepared and purified in a Finnish laboratory and supplied by the NIAID Antiviral Substances Program. During the three trials, three different dosages were given to 45 patients for seven to eight days, beginning on the first or second day of the infection.

(more)

INTERFERON (CONT'D)

The best results were seen in patients who were treated early in the infection and who received the highest dosage of interferon. No cutaneous dissemination of the zoster infection occurrred in these patients and the duration of pain was shortened. No visceral complications occurred in patients who received the two highest dosages. One patient of the group who received the lowest dosage developed a visceral complication; six of the 45 placebo-treated patients developed these complications. Side effects were few.

These promising results emphasize the need for the development of a way to produce larger quantities of interferon for broader studies.

Drs. Merigan, Kenneth H. Rand, Richard B. Pollard, Paul S. Abdallah, George W. Jordan, and Richard P. Fried published their results in the May 4 issue of the *New England Journal of Medicine.*

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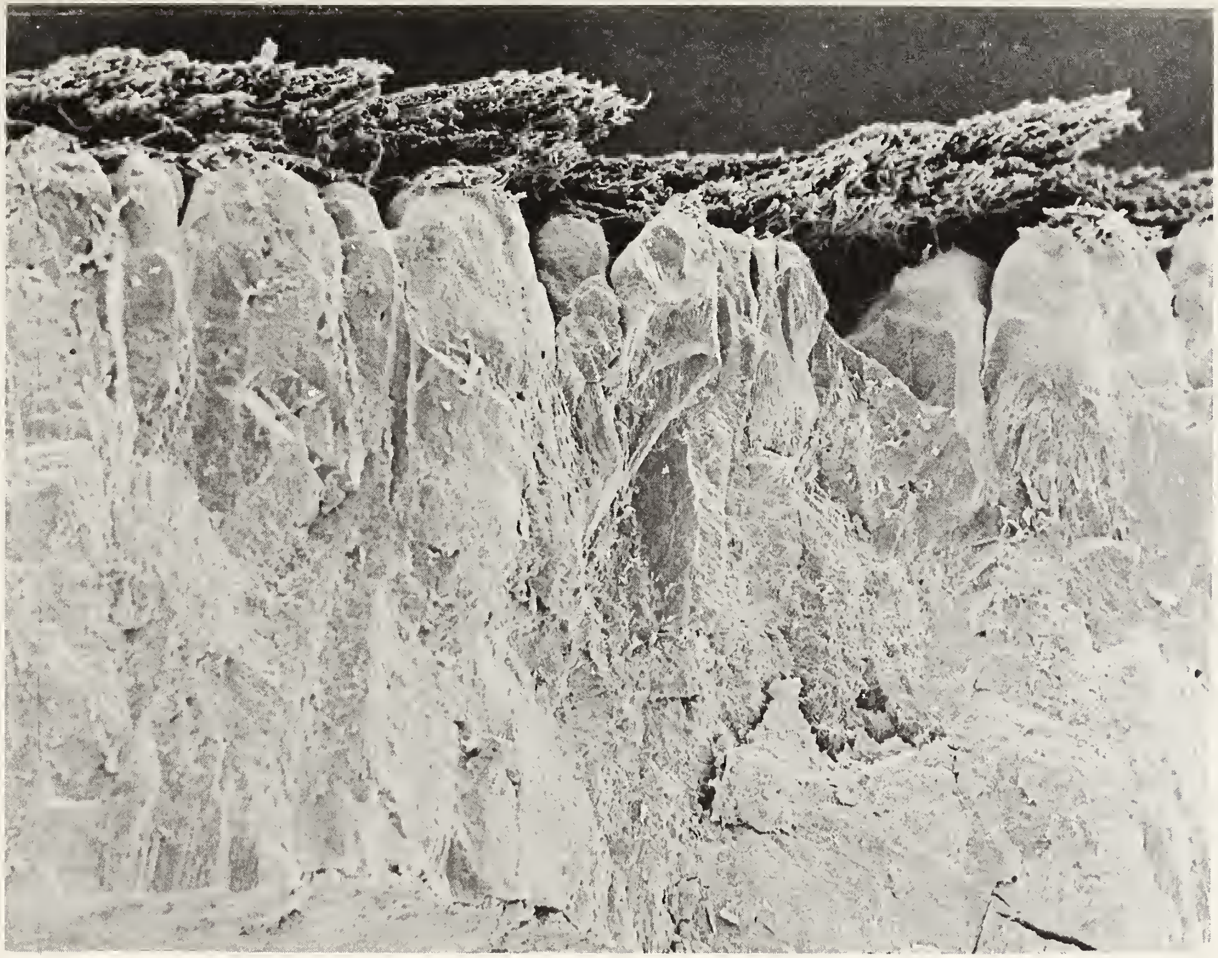
WHAT IS IT? WOULD YOU BELIEVE AN EGG SHELL?



Rugged cliffs topped by thick mass of brush or dwarf trees? Wrong! This is a micrograph of a fractured chicken egg shell magnified 1,200 times by a scanning electron microscope at the Oregon Regional Primate Research Center in Beaverton. The photo was taken by Dr. Wolf H. Fahrenback, head of the Laboratory of Electron Microscopy at the Center which is supported by N I H's Division of Research Resources. The "cliffs" ***represent the actual edge*** *of the broken shell, and the brush on top is the skin-like layer (ovokeratin layer) one encounters when cracking an egg. (NIH Photo #1614)*

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August 1978

NEWS & FEATURES From NIH

NIAID EXPANDS ITS EFFORTS IN INTERNATIONAL HEALTH

NIH's National Institute of Allergy and Infectious Diseases (NIAID) is expanding its efforts in international health by assisting research centers in developing countries, and by encouraging and strengthening scientific linkages between the U.S. and foreign investigators. These new efforts will consist of two interrelated activities: International Program Projects Grants and International Exploratory/Developmental Research Grants.

The programs will emphasize research related to medical problems important to developing countries. NIAID is interested in research on tropical diseases involving medical protozoology, entomology, helminthology, malacology, mycology, virology, and bacteriology. Special attention will be given to infectious diseases, including those emphasized in the WHO Special Program for Research and Training in Tropical Diseases -- malaria, schistosomiasis, filariasis, trypanosomiasis, leishmaniasis, and leprosy. However, the program does not exclude other disease categories equally important to developing countries.

International Program Projects Grants will be aimed at establishing a program in International Collaboration in Infectious Diseases Research (ICIDR) that will link U.S. institutions to research units at overseas sites. These grants, which will replace the current International Centers for Medical Research (ICMR), focus on infectious diseases and the immunology of these diseases. A major portion of the research must be conducted in a foreign country, and it must be relevant to one or more important health problems of that country.

Through the International Exploratory/Developmental Research Grants, NIAID will be encouraging additional linkages between U.S. and foreign

(more)

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INTERNAT'L. HEALTH (CONT'D)

investigators with common research interests in infectious diseases and immunology. Considered under this arrangement will be receipt of individual research proposals from a U.S. investigator involving collaboration with a foreign affiliate at a overseas site. Purpose of the collaboration will be to identify and investigate common areas of interest in infectious diseases and the immunology of these diseases. However, these grants are not intended to provide long-term support but, rather, to encourage the development of program project grants.

Prospective applicants for one or both of the International Programs may submit a letter of intent for program information on or before November 1, 1978. However, this letter is not a prerequisite to submitting a grant proposal.

Application kits containing a special format with accompanying instructions for each of the new programs are available from:

Dr. Earl S. Beck, Special Assistant to the Director
Microbiology and Infectious Diseases Program
National Institute of Allergy and Infectious Diseases
Room 749, Westwood Building
Bethesda, Maryland 20014

Requests for additional information relating to these grants may be obtained by writing to the above or by telephoning Dr. Beck at (301) 496-7065.

In addition, details of these International Programs are provided in the May 12, 1978 issued of *NIH Guide for Grants and Contracts*, Vol. 7, No. 7.

Deadline for receipt of proposals has been set for January 15, 1979.

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August 1978

NIH WILL OFFER TRAINING FOR TEACHERS ON SICKLE CELL DISEASE

Starting in 1979, the National Institutes of Health will offer special training seminars on sickle cell disease for high school health and science teachers.

The program will be coordinated by the Sickle Cell Disease Branch, National Heart, Lung, and Blood Institute. Its purpose is to facilitate the understanding of sickle cell disease and related conditions among high school students through active participation of local teachers.

Seminars, each lasting for one or two days, will be offered in cities across the nation where local teachers and education administrators have expressed interest in the program and commitment to its goals. Each seminar will accommodate up to 50 teachers sponsored by local education agencies. Inquiries or expressions of interest in participating in the program are invited.

A "workshop" format will be used to present current concepts about genetically-transmitted conditions affecting red blood cells. Sickle cell trait and sickle cell disease, probably the most prevalent of these conditions, will be used as the teaching model, with emphasis on genetics, probabilities of transmission by affected individuals to their children, testing procedures, and clinical manifestations.

Qualified health professionals will conduct seminar sessions in specific subject areas, using curriculum plans, study guides, and teaching aids specially developed for the program and adaptable to varying needs of different client audiences.

The seminars will be free, except for transportation costs or incidental

(more)

SICKLE CELL (CONT'D)

expenses incurred by participants or sponsoring agencies.

Those interested in participating in the program or desiring further information about it should write to: Teachers Training Seminars, Sickle Cell Disease Branch, NIH, Building 31, Room 4A-29, 9000 Rockville Pike, Bethesda, Maryland 20014.

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Editors of publications may request a glossy print of the numbered photographs that appear in this issue.

Mrs. Joyce F. McCarthy
National Institutes of Health
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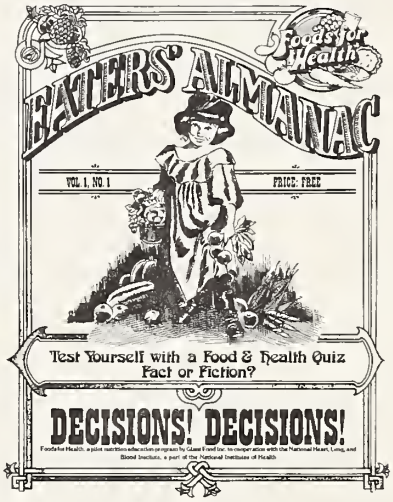
NEWS&FEATURES FROM NIH

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE ■ Public Health Service ■ National Institutes of Health ■ Office of Information ■ Bethesda, Maryland 20014



Foods for Health
EATERS' ALMANAC
VOL. 1, NO. 1
PRICE: FREE
Test Yourself with a Food & Health Quiz Fact or Fiction?
DECISIONS! DECISIONS!
Foods for Health, a pilot nutrition education program by Giant Food Inc. in cooperation with the National Heart, Lung, and Blood Institute, a part of the National Institutes of Health

See page 18

October 1978

RESEARCH ADVANCES:

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TOBACCO ALLERGY MAY CAUSE HEART ATTACKS

Tobacco allergy may significantly increase the incidence of heart attack in cigarette smokers, particularly in younger smokers. These are the speculative observations of Dr. Carl G. Becker and Dr. Theodore Dubin in research supported in part by NIH's National Heart, Lung, and Blood Institute.

The investigators at Cornell University Medical School found that one-third of healthy smoking and non-smoking volunteers exhibited immediate wheal-and-flare skin reaction to a glycoprotein antigen extract purified from cured tobacco leaves and cigarette smoke condensate.

The Framingham study has observed that younger smokers are at relatively greater risk of suffering heart attacks than older smokers. A possible explanation of this apparent anomaly is that among younger smokers are a certain number who are hypersensitive or allergic to tobacco smoke. Repeated immunologic challenge of cigarette smoking in this group may cause accelerated cardiovascular disease and increased mortality.

Previous attempts at establishing tobacco allergy have found varying rates of incidence, from one-fourth to one-third in smokers and non-smokers. These studies were challenged, however, on the lack of purity in the antigen extract used and the lack of evidence that antigens extractable from tobacco leaves are also present in tobacco smoke.

Using means for purification that have only recently become available, the Cornell investigators prepared two extracts, one from cured tobacco leaves, the other from cigarette smoke condensate.

The flue-cured tobacco leaves were powdered, deflated, and extracted in a physiologic saline solution. The extract was clarified by filtration and centrifu-

(more)

gation, then precipitated and powdered. The powder was redissolved and applied to a molecular sieving column to remove any small pharmocologically active molecules such as nicotine. The remaining brown fraction was then subjected to continuous flow electrophoresis in an alkaline gel column. The cigarette smoke condensate was treated in the same manner as the tobacco leaves.

The material purified from the tobacco leaves and from the cigarette smoke formed identical bands in the electrophorised gel and both took the Coomasie blue stain, indicating they were glycoproteins. The researchers estimated the molecular weight of the tobacco glycoprotein to be approximately 18,000 daltons.

They labeled the tobacco leaf extract as TGP-L and the cigarette smoke condensate as TGP-CSC. Testing in rabbits established that the two glycoprotein extracts were immunochemically similar.

Thirty-one healthy volunteers, 15 smokers and 16 non-smokers, were then inoculated intracutaneously with two micrograms of TGP-L in sterile saline solution. Within 20 minutes, wheal and flare skin reactions occurred in 12 of the volunteers, six from each group. No reaction was found in an inoculation of sterile saline used as a control.

A volunteer reactive to TGP-L was given TGP-CSC and a wheal-and-flare reaction occurred. Conversely, a volunteer who did not react to the TGP-L also did not react to the TGP-CSC. Thus approximately one-third of the volunteers exhibited immediate skin reaction to highly purified tobacco antigen, this response presumably mediated by IgE (allergy) antibodies. This high incidence of allergic reaction is comparable to other investigations using a less-purified antigen preparation.

(more)

TOBACCO (CONT'D)

The investigators estimated that cigarette smoke condensate tar contains 1 to 4 micrograms of antigen per milligram. Smoking one pack of 20 cigarettes with 20 mg of available tar per cigarette would thus expose the smoker to 400 micrograms of antigen. As a comparison, it is estimated that the total amount of ragweed antigen inhaled during the entire pollination season in Baltimore is less than 0.9 micrograms per adult. The amount of TGP is cigarette smoke would therefore seem sufficient to sensitize even non-smokers vicariously.

Another possible mode of sensitization is through consuming cross-reacting antigens which the investigators identified in potatoes, tomatoes, green pepper, and eggplant, all close relative of tobacco in the family *Solanaceae.*

Two possible modes of tobacco allergy accelerating cardiovascular disease are posited by the researchers. One is that the allergic smoker who repeatedly used tobacco stimulates the IgE mediated release of vasoactive histamines within the bloodstream from basophils and platelets. This would render the blood vessels more vulnerable to focal injury by immune complexes and more permeable to lipoproteins, thus increasing the rate of arterial scarring and cholesterol deposition. A protracted form of vessel injury may occur culminating in cardiovascular disease, or possibly pulmonary disease from debilitated pulmonary vessels.

Another possibility is that tobacco allergy may interfere directly with the function of the heart itself. Research in penicillin allergy found that when sensitized guinea pigs were challenged with penicillin protein conjugates, ventricular fibrillation was the terminal event in half of the anaphylactic deaths.

That cigarette smoking is associated with substantially higher risk of cardiovascular disease is unquestioned. The research reported here proposes

(more)

TOBACCO (CONT'D)

one provocative explanation for that increased risk. However, this is a preliminary report, and it should not be interpreted as proof but as a possible mechanism. Further confirmation is necessary before any one mechanism can be accepted as the cause of the demonstrated greater risk of cardiovascular disease.

These results were published in the August 1978 issue of *Cardiovascular Disease*.

#

CANCER INCIDENCE FOR U.S. WOMEN INCREASES

HEW's National Cancer Institute (NCI) has published SEER Program: Cancer Incidence and Mortality in the United States, 1973-76, a report that provides baseline rates for cancer occurrence and deaths in the United States for the 15 most common cancers. The data are based on reports from 11 population-based cancer registries that monitor approximately 10 percent of the United States population. Complete mortality data for the entire U.S. population is published by the National Center for Health Statistics.

Incidence (occurrence) rates in the new report are not precisely comparable with previous NCI-reported rates because of some differences in the populations sampled. However, the new rates suggest an annual increase in incidence, from 1970 through 1976, of one to two percent, with white females showing the greatest increase - just under two percent.

The increase in women was due largely to a striking eight percent annual increase in lung cancer incidence for white women and almost ten percent for black women. An increase in breast cancer incidence was noted late in 1974, but dropped in subsequent years, due possibly to earlier diagnoses of breast cancers in women following increased publicity about the disease. Women, both white and black, showed an increase in cancer of the endometrium, or body of the uterus, almost as large as the lung cancer increase. Cancer of the uterine cervix continued to decline in both white and black women.

Lung cancer incidence increased approximately one percent annually among white males and four percent annually among black males, reflecting in part the unusually high rates among men in New Orlenas. White males showed a slight increase in incidence for prostate cancer, and stomach cancer rates

(more)

continued their decline in both sexes.

The average annual incidence rate for the years 1973-76, for all SEER areas excluding Puerto Rico, for all cancers combined was 324.4 per 100,000 population. This average reflected rates ranging from 277.8 in Utah to 358.0 in San Francisco. The rate for Puerto Rico was much lower, 200.7, reflecting the lower overall rates among Spansih speaking populations.

For all SEER areas combined, cancers of the colon and rectum, breast, and lung and bronchus showed the highest annual rates. Incidence and mortality (death) rates per 100,000, respectively, for cancers of the colon and rectum combined were 47.2 and 22.3; for breast cancer, 46.3 and 15.0; and for cancer of the lung and bronchus, 45.2 and 36.9. For other forms of cancer, incidence rates were substantially lower.

The SEER reporting system (Surveillance, Epidemiology, and End Results) was established in 1973 to analyze the scope of the cancer problem in the United States. It is a consolidation of two earlier NCI programs that reported incidence via periodic surveys and survival via annual monitoring of cancer patients by selected hospital-based cancer registries.

For the first time, the NCI has reported incidence and mortality rates for the same populations. These rates are adjusted to the 1970 age-sex-race distribution of the U.S. population. The report also provides information for the first time on Puerto Rico and the Spanish-origin population of New Mexico. All rates are based on population estimates provided either by the Bureau of the Census or local sources. Data for the mortality rate calculations were provided by the National Center for Health Statistics.

(more)

CANCER (CONT'D)

Areas covered by SEER are metropolitan Atlanta, Detroit, New Orleans, and San Francisco; Seattle-Puget Sound, comprising 13 counties; the entire states of Connecticut, Hawaii, Iowa, New Mexico, and Utah; and the Commonwealth of Puerto Rico. The populations in these areas comprise slightly more than 10 percent of the total U.S. population, and their mortality rates for the 15 major cancers are close to the total U.S. experience.

For example, the average annual mortality rate for all cancers combined was 165.8 per 100,000 for the four years covered by the report; the comparable rate for the SEER areas was 167.7. For cancer of the colon and rectum, the U.S. mortality rate was 22.3; for SEER areas the rate was 22.7. For breast cancer, the U.S. and SEER rates were 27.0 and 28.3, respectively for white women; for black women the rates were 26.2 and 27.2.

NCI scientists believe the incidence rates for cancer also represent the experience of the U.S. as a whole, although the SEER participants were selected more to provide insight into the cancer experience of specific population subgroups than as a random sampling of the U.S. population.

For New Mexico, NCI scientists noted higher incidence for lung and colon cancers among Anglo males, while Spanish males showed higher stomach cancer rates. Because of the relatively small numbers of cancer cases in the comparisons, however, these differences will be reexamined as more data are gathered.

The report also provides provisional three-year relative survival rates for white patients with cancers of the lung and bronchus, breast, colon and prostate from the five SEER registries that have compiled adequate data

(more)

CANCER (CONT'D)

since 1973 to produce reliable rates. Relative survival is an adjustment of observed survival for deaths due to causes other than cancer. Further analyses according to extent of disease are being carried out.

Women experienced an average 78 percent three-year relative survival after diagnosis of breast cancer. Both sexes combined showed 12 percent three-year survival after diagnosis of lung cancer and 49 percent of the patients diagnosed with colon cancer survived three years or more. Men showed 68 percent three-year survival after diagnosis of cancer of the prostate.

Future publications will update the incidence and mortality statistics and provide more detailed survival information for the same populations. Over a period of time, the SEER reporting system should enable NCI scientists to analyze trends in incidence, mortality, and survival of the same populations in more detail.

Single copies of SEER Program: Cancer Incidence and Mortality in the United States, 1973-76, DHEW Publication No. (NIH) 78-1837, are available from the Office of Cancer Communications, National Cancer Institute, Bethesda, Maryland 20014.

#

SPLEEN SHOWN MAJOR ORGAN INVOLVED IN MALARIA

Researchers at NIH's National Institute of Allergy and Infectious Diseases (NIAID) have shown, for the first time, that the spleen is the major organ involved in the removal of malaria-infected red blood cells (RBCs) from the bloodstream and that this removal does not appear to depend on antibodies. Furthermore, results of their animal studies -- presented October 4, 1978, at the 18th Interscience Conference on Antimicrobial Agents and Chemotherapy -- indicate that, during malaria, this function of the spleen is impaired.

A major constituent of the body's defense system, the spleen can remove invading organisms by immunologic mechanisms (involving antibodies) as well as non-immunologic ones (non-specific trapping of particles). However, no one has previously examined in detail the processes by which RBCs containing malaria parasites are removed from the circulation. Several findings, including the detrimental effect which removal of the spleen has on malaria infection, have suggested a possible role for the spleen in the defense against this disease which, despite all efforts, continues to claim more than a million lives annually.

To investigate whether clearance of infected RBCs by the spleen is a major defense mechanism, Drs. Thomas C. Quinn and David J. Wyler used rats infected with a non-lethal strain of *Plasmodium berghei*. This is a rodent malaria in which the host spontaneously "cures" itself of the infection and within 20 days, no parasties can be detected in the blood. RBCs infected with this parasite were treated with a radioactive chemical and injected into rats immune to *P. berghei* (those which had recovered from the disease) and normal rats.

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During the first hour, infected RBCs were removed from the circulation of the immune rats three times more rapidly than in the normal ones; thereafter, the clearance rates were similar. This difference is the result of a greater uptake of the cells by the greatly enlarged spleens of the immune rats.

To determine the type of mechanism involved, the scientists then injected radioactive non-infected RBCs coated with an antibody into immune and normal rats. Both groups of animals cleared these cells at a similar rate, suggesting that the splenic process in malaria-infected rats is not antibody-dependent. In addition, hyperimmune serum, taken from *P. berghei* immunized rats, had no effect on clearance of infected RBCs in the normal rats.

Next, the researchers compared the clearance rate of the malaria-infected RBCs with RBCs containing another type of intracellular particle. These Heinz bodies, as they are called, are clumps of denatured hemoglobin trapped within the RBC and which, therefore, decrease the cell's ability to alter its shape and so "squeeze" through narrow openings in certain areas of the spleen. Since malaria-infected RBCs also have this problem, the Heinz body-containing RBCs simulate several non-immunologic properties of the parasitized cells.

Clearance of these Heinz body RBCs was found to be similar to that of infected RBCs: the clearance was by the spleen and the rate was directly related to the organ's size. Thus, the scientists conclude that removal of the parasitized RBCs by the spleen may be related to the cells' decreased ability to flow easily through the organ's narrower passageways rather than to an immune process.

Additional studies show that the clearance of parasitized RBCs is slower

(more)

SPLEEN (CONT'D)

in rats with an active malaria infection than in immune and normal rats. This appeared to result from the spleens' impaired ability to sequester the RBCs, despite the fact that the spleens were enlarged. However, the onset of spontaneous resolution of the infection was associated with increased clearance and splenic uptake which exceeded that found in the immune or normal rats.

These results indicate that the spleen is the major organ that determines the clearance of infected RBCs. During rising parasitemia early in infection, splenic clearance of these cells is depressed. Later, as the animal begins to resolve the infection, unknown events occur which increase the spleen's ability to clear these cells. Thus, the Bethesda scientists believe that other mechanisms, in addition to clearance of infected RBCs, are important in host defense in malaria.

#

NEW TEST IDENTIFIES CYSTIC FIBROSIS CARRIERS

by Tina McIntosh

Presently, there is no reliable method for detecting carriers of Cystic Fibrosis (CF) or for making intrauterine diagnosis of this condition. Recently, however, scientists have discovered a clue that may lead to detection of carriers (heterozygotes) for CF and prenatal diagnosis of this autosomal recessive disease that affects mostly Caucasian children (CF occurs once in every 1600 to 2500 live births).

Harvard researchers partially supported by the National Institute of Child Health and Human Development have observed that skin cells cultured from individuals with CF are more resistant than normal cells to the cytotoxic effects of dexamethasone, a synthetic steroid hormone (glucocorticoid) that stimulates the production of glucose in the liver. Cultured fibroblasts from known CF carriers have an intermediate survival rate compared with normal and homozygous CF cells (cells from persons with CF).

In addition, analysis of cells taken from the amniotic fluid of a pregnant woman who is a known carrier of CF revealed considerable dexamethasone resistance. This resistance was lacking in cells derived from the amniotic fluid of a pregnant woman who did not carry the trait for CF.

In a total of 73 drug survival assays, 24 cell strains were tested: 7 homozygous for CF, 9 known heterozygous, and 8 normal. Cells from a normal study participant, a heterozygote, and a homozygote were tested in each of the 73 assays.

Even though these experiments suggest that assays with dexamethasone may eventually be useful in prenatal diagnosis of CF and in detecting carriers for CF, the investigators point out that many more tests are needed before

(more)

clinical reliability of the technique is established. The dexamethasone assay must also be refined before heterozygote detection is possible.

Currently, CF is diagnosed by analyzing the prespiration of persons suspected of having the disease as CF victims have a higher-than-average amount of salt in their sweat. Despite widespread use of this diagnostic technique, the disease is often undetected in young children until symptoms become severe. (Some of its common symptoms are coughing, wheezing, and foul-smelling stools).

CF affects the exocrine glands. The disease particularly affects the sweat, saliva, tear, and mucus-producing glands causing the latter to secrete a thick, sticky mucus rather than a normal, clear, free-flowing fluid. This abnormal mucus accumulates in various body systems, interfering with the normal functioning of the affected parts, most often the gastrointestinal and respiratory systems. For instance, digestion of food is difficult because mucus blocks the pancreatic ducts, impairing metabolic processes. Consequently, children with CF are frequently small for their age, although many have seemingly insatiable appetites.

Other common problems that affect most of those afflicted with the disease include difficult breathing and respiratory infections. The thickened mucus in the lungs becomes a medium for infection, blocks the air sacs, and decreases lung capacity. Lesser known effects of CF are peptic ulcers, sinus trouble, polyps in the nose, and sterility in males. But the earlier the diagnosis of Cystic Fibrosis, the better the quality of life because prompt detection allows treatment to begin immediately, delaying or lessening the

(more)

damage the disease does to the body. Equally important, intrauterine diagnosis of the disease would permit prompt treatment after birth and provide the prospective parents of an affected child with the opportunity to take advantage of genetic counseling.

Other NIH agencies that provide partial support for research, as reported in *Science*, Vol. 201, are the National Institute of Arthritis, Metabolism, and Digestive Diseases and the National Heart, Lung, and Blood Institute. The researchers are J. L. Breslow, J. Epstein, J.H. Fontaine, and G.B. Forbes with the Department of Medicine, Children's Hospital Medical Center, and the Department of Pediatrics, Harvard Medical School, Boston, Massachusetts.

###

NIH CONSENSUS REACHED ON EMERGENCY TREATMENT OF INSECT STING

The NIH Consensus Development Conference on Emergency Treatment of Insect Sting Allergy considered the epidemiology, morbidity, and mortality of anaphylactic reactions to insect stings (*Hymenoptera and Solenopsis*, or fire ants), evaluated the availability and effectiveness of therapy by health-care professionals and others, and determined whether undue delay in reaching definitive care contributed importantly to morbidity.

Convened on September 14 and 15, 1978 at NIH, the panel discussed whether changes in the current mode of management should be recommended, possibly including broader availability of "insect sting kits" containing injectable epinephrine, antihistaminic tablets and a tourniquet. A summary of the panel recommendations follows:

The panel recognized that everyone is a potential victim of life-threatening or fatal allergic reactions from stinging insects. Although the panel realized that valid data regarding the incidence of these occurrences are not available at this time, the data presented to the panel suggest that such allergic reactions occur with greater frequency than is generally thought. Prior identification of those individuals who will so react is difficult. The panel believes that better education of the lay and professional populations will improve documentation of these events and tend to promote immediate and effective medical treatment, which can prevent the majority of fatalities.

Reducing the size of the problem requires two approaches. The educational approach entails instructing both laymen and professionals on the dangers of insect stings and on the means to treat them. The service approach entails increasing the availability of treatment--to the maximum extent permitted by

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law--by encouraging and allowing all personnel who are properly trained to administer such emergency treatment at the site of the emergency.

The belief that certain individuals are restricted from providing treatment may be based less on the applicable law than on misunderstanding of the state of law in this area. Given the objective of increasing the availability of emergency treatment, the panel encourages evaluation of the legal risks, placing them in the proper perspective.

Teaching films and written materials for the lay public should be developed and distributed to help promote recognition of the problem of anaphylactic reactions to insect stings and to make known the available therapeutic regimens. These should be disseminated by interested organizations such as school and parent organizations, youth groups, farmers, industrial and labor organizations, and other groups whose members are at high risk. We urge that people allergic to insect stings use available methods to identify their sensitivity to others.

Education of physicians should include information on emergency management of systemic reactions, emergency drugs, and the use of immunotherapy (hyposensitization). Physicians and other health-care personnel should instruct patients about the importance of avoiding insect stings and about the treatment of life-threatening reactions to such stings. Warnings should be given about the possibility of adverse drug interactions.

The panel considered and rejected the option of making insect sting treatment kits--containing a predetermined dose of epinephrine for injection--available as an over-the-counter product. In the absence of individualized instruction for its administration, the panel believes there is considerable

(more)

INSECT STING (CONT'D)

potential for inappropriate use of the kit by individuals with hypertension, certain cardiovascular disease, or those who are taking certain medications. The panel believes these concerns would not be addressed adequately by labels or printed instructions that might be required for an over-the-counter item. The drug abuse potential for such kits was also of great concern.

Research is needed to determine whether there may be other drugs and/or modes of administration that would be more effective and safer than current methods.

#

CONSUMER EDUCATION RESEARCH PROGRAM LAUNCHED

"Foods for Health," a pilot nutrition education research program designed to help consumers make informed choices at the supermarket was launched October 17, 1978, by NIH's National Heart, Lung, and Blood Institute (NHLBI), in cooperation with Giant Food, Inc.

This year-long pilot program will offer shoppers, at 90 Giant supermarkets in the Washington, D.C. area, the most current information on nutrition and heart research findings. Every two weeks different heart-health issues as well as practical shopping tips and food preparation suggestions will be presented in the stores through pamphlets called *Eaters' Almanac*, shelf signs, and posters. Giant's consumer radio spots and newspaper advertising will also contain heart health messages.

According to Dr. Robert I. Levy, NHLBI Director: "Evidence continues to mount that there is a definite relationship between nutrition and coronary heart disease. All the answers are not in. Where scientifc consensus is lacking on heart nutrition issues, consumers will be informed on what current evidence exists as well as what questions remain unanswered. Responsibility for deciding whether to change food selection will obviously rest upon the consumers, but they are encouraged to use the heart-health information materials in their decision making. We need to evaluate how we can effectively communicate this information to the American public. Projects like "Foods for Health" which reach the consumer where food selections are made may play a leading role in the future control of diseases."

NHLBI scientists will evaluate the program's effectiveness by analyzing: 1) changes in consumer knowledge of nutrition and food preparation as it

(more)

relates to coronary heart disease and 2) overall changes in food selection available from Giant's computer-assisted check out system data. The data from Washington area Giant stores will be compared to that from comparable non-participating Giant stores in the Baltimore area.

Odonna Mathews, Consumer Advisor to Giant Food, Inc. said: "Over the past couple of years, we've become increasingly aware of the consumers' growing interest in nutrition and health issues. Giant Food is committed to helping consumers make informed decisions. We are particularly pleased to sponsor this program. We hope that it will show effective ways to communicate information about nutrition and health, especially heart health, to consumers."

This pilot program reflects NHLBI's Congressional mandate to provide the American public with information about heart research findings, and encourage individual life-style changes that may contribute to better health.

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EDUCATION (CONT'D)

"Foods for Health" dairy aisle display with *Eaters' Almanac* *in a Giant Food Store. This nutrition education research program was designed to help consumers make informed choices at the supermarket sponsored by NIH's National Heart, Lung, and Blood Institute and Giant Food, Inc. (NIH Photo # 1615)*

October 1978

EWS & FEATURES From NIH

FOUR IMMUNOLOGY RESEARCH CENTERS ESTABLISHED

Dr. Richard M. Krause, Director of NIH's National Institute of Allergy and Infectious Diseases (NIAID), has announced the establishment of four Centers for Interdisciplinary Research on Immunologic Diseases.

The work of the Centers will be concerned with research, patient care, and postgraduate education. They are at the University of Rochester Medical Center, N.Y.; Georgetown University School of Medicine, Washington, D.C.; the University of California at Los Angeles; and Washington University School of Medicine, St. Louis.

A total of $900,000 was set aside by Congress to establish a new program which seeks to encourage interdisciplinary research in immunologically-mediated and allergic diseases including asthma. This includes money for grants and administrative costs. The overall objective of the Centers is to accelerate the clinical application of new knowledge on the immune system and its disorders deriving from studies in basic biomedical sciences and medical specialties.

Investigations at Rochester will be headed by Dr. John P. Leddy, Professor of Medicine and Microbiology. This Center will examine the biologic and genetic aspects of human complement (a complex series of blood proteins involved in immune responses) and will characterize the human autoimmune response in which antibodies are developed against the body's own antigens. Research will also be aimed at studying asthma and rhinitis (inflammation of the mucous membrane of the nose) utlizing biochemical techniques. There also will be a prospective study of the relationship of recurrent lower respiratory tract disorders in infancy to the development of asthma in adults.

The research at the Georgetown University School of Medicine will be

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directed by Dr. Joseph A. Bellanti, Professor of Pediatrics and Microbiology. Investigations will be grouped into four major areas: an Allergic Diseases and Respiratory Program includes a project focusing on regional socio-economic impact of immunologic diseases, particularly asthma; the Infectious Diseases Program is aimed at developing a live vaccine directed against *Haemophilus influenzae* type b, a common bacterial agent of respiratory infections; an Immune Regulatory Program will concentrate on producing reagents for use in study of autoimmune diseases; and research in the Immunopharmacologic Program will study the role of certain skin cells in various skin diseases and skin graft rejection.

The Center located at the University of California School of Medicine, Los Angeles, will be headed by Dr. John L. Fahey, Professor and Chairman of the Department of Microbiology and Immunology. The research at this Center will include immune functions in various immunologic diseases and investigations on possible relationships of genetic markers to such abnormalities. One project will explore developmental changes governing the onset of allergic reactions in young children. Another project will focus on a suspected defect in a regulatory mechanism that limits antibody production in such autoallergic diseases as rheumatoid arthritis and systemic lupus erythematosus. An educational program emphasizing self-management of asthma will be initiated for children with this condition and their parents.

Dr. Charles W. Parker, Professor of Medicine, Microbiology and Immunology, will head the Center at Washington University School of Medicine. Studies will focus on the control of immunologic inflammation through analyses of

(more)

CENTERS (CONT'D)

biochemical and cellular events. This Center will investigate the early biochemical events in white blood cell activation and the alteration of white blood cell function in human diseases, particularly in inflammatory bowel disease. Research will also be conducted on the role of certain cells -- mast cells -- in the tissue destruction characteristic of some immunologic skin diseases. In addition, efforts will be directed toward characterization of the receptor for IgE -- the allergic antibody -- located on the surface membrane of human and animal mast cells and basophils (white blood cells that contain histamine).

#

NEW NIGMS BOOKLET EXPLAINS "INSIDE THE CELL"

The achievements of modern cell biology are examined in a new 96-page booklet, *Inside the Cell,* published by NIH's National Institute of General Medical Sciences (NIGMS). The booklet contains more than 50 illustrations, and explains the history and description of the incredibly complex world within the living cell.

Separate chapters are devoted to the tiny organelles within cells such as the nucleus, ribosomes, endoplasmic reticulum, Golgi apparatus, lysosomes, and mitochondria, without which life would not be possible. Special attention is focused on the surface or plasma membrane, through which a cell regulates its own internal environment with great precision. In addition, recent discoveries are described that link specific cellular abnormalities to specific disease processes, producing entirely new concepts for medical treatment and prevention.

Greater knowledge of the cells that make up our bodies and of the myriad factors that regulate their activities and interrelationships has, accordingly, become a major goal in the nation's efforts to combat disease and affliction. As Nobel Prize-winning scientist Christian de Duve of Rockefeller University explains, "We are sick because our cells are sick. We cannot make ourselves well unless we know what is happening inside."

Free single copies of *Inside the Cell* can be obtained from NIGMS, Westwood Building, Room 9A-05, Bethesda, Maryland 20014, which has the primary responsibility for advancing research in sciences basic to medicine.

The booklet will be of special value to high school science teachers and students. Others will find it useful as a summary of new developments in one

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BOOKLET (CONT'D)

of the most rapidly developing areas of the health sciences.

INSIDE THE CELL

The New Frontier of Medical Science

Series: A New Medical Science for the 21st Century

#

COMPUTER DISPLAYS 3-D MOLECULAR GRAPHICS

An NIH physician-scientist and a computer specialist demonstrated various current and potential uses of the computer in biomedical science during a Science Writers Seminar held at the National Institutes of Health in Bethesda, Maryland on October 12, 1978.

"Molecular graphics," a visual approach to studying biochemical molecules, was demonstrated by William C. Mohler, M.D., and Richard Feldmann, M.S.E.E., of NIH's Division of Computer Research and Technology, with the screening of a short film made with programmer Thomas K Porter. The film showed 3-dimensional computer views of gamma globulin, an antibody molecule critical in the defense against disease. The computer film was produced from calculations of angles of atoms in the antibody molecule, and the distances between the atoms. This key information was provided from X-ray crystallographic data developed by the Molecular Structure Section of the Molecular Biology Laboratory at NIH's National Institute of Arthritis, Metabolism, and Digestive Diseases.

Other molecular features illustrated by Dr. Mohler and associates via 3-dimensional computer graphic techniques included the active sites of ribonuclease (an enzyme that digests one of the cell's genetic chemicals called RNA) and of carbonic anhydrase (an enzyme that facilitates the transport of carbon dioxide out of the body).

Dr. Mohler explained that the structural features of important biological molecules have been made more accessible to scientists and students by an "Atlas of Macromolecular Structure on Microfiche" developed by Mr. Feldmann under an NIH contract. With the Atlas' stereo viewer and 3-D glasses, microstructures of sixty-nine nucleic acid and protein molecules, including

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GRAPHICS (CONT'D)

heme proteins, peptide hormones, proteases, lectins, and carbohydrases can be viewed.

More recently, Mr. Feldmann extended the system to an inexpensive cardboard viewer and stereo pairs of color slides affordable by many high school science students.

Dr. Mohler, who is Associate Director of the Division of Computer Research and Technology (DCRT), also reviewed "radionuclide cineangiography" of the heart. This is a method by which computer images build a picture of heart function, or malfunction, throughout its pumping cycle. He showed a film that demonstrates the technique's usefulness in identifying persons with weakened heart walls. He noted that the technique resulted from long-term collaboration by DCRT scientists with Michael V. Green and Stephen L. Bacharach, Ph.D., in the Nuclear Medicine Department of NIH's Clinical Center, and later was applied clinically by Jeffrey S. Borer, M.D., of the National Heart, Lung, and Blood Institute.

Dr. Mohler said a similar technique is being used by Bruce R. Line, M.D., of DCRT to visualize the functioning of human lungs in health and disease. Dr. Line is conducting this research in conjuction with the Nuclear Medicine Department of NIH's Clinical Center, and Dr. Ronald Crystal of the National Heart, Lung, and Blood Institute.

In discussing the overall role of the Division of Computer Research and Technology, which is the world's largest biomedical computing facility, Dr. Mohler stressed the importance of long-term development projects involving DCRT staff and the scientists of the other NIH Institutes and Divisions. For

(more)

example, he noted that DCRT is collaborating in research to utilize data collected by the computerized axial tomography scanners and the computerized Medical Information Systems.

DCRT is also working on several developmental projects that can be described as "systems looking for applications." One such project is a "voice-answer-back" system that uses a microcomputer to convert written text instantaneously into voice sounds that are understandable. To date this work, conducted by the Computer Systems Laboratory of DCRT, has been primarily of interest to persons and organizations attempting to develop a device that will serve as a reader for blind persons.

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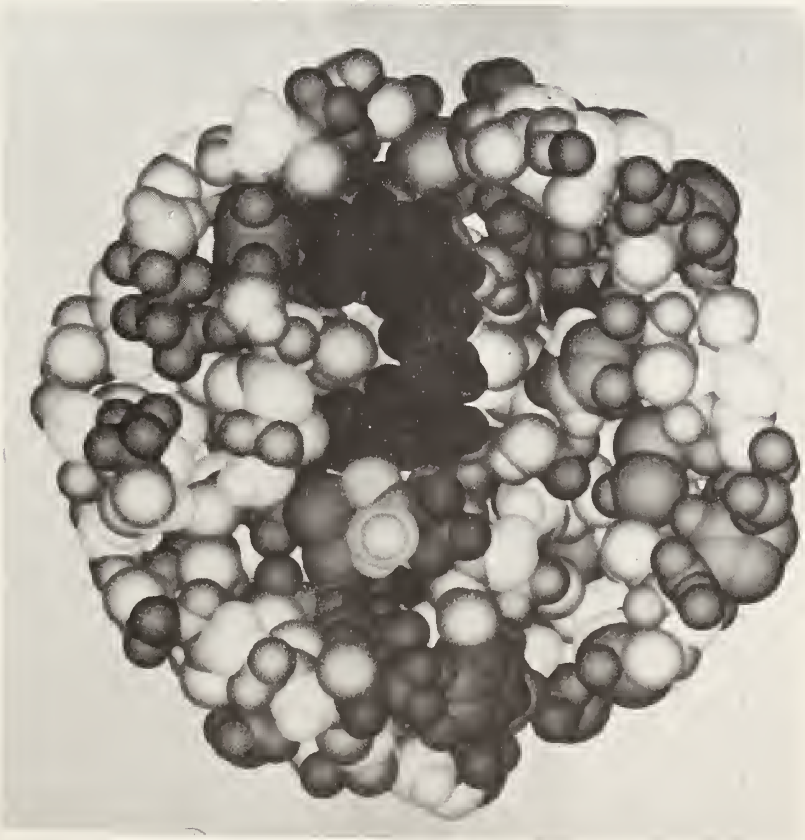
GRAPHICS (CONT'D)

Available for less than two dollars, this inexpensive cardboard viewer enables science students to study molecular structures in three dimensions. (NIH Photo #1617)



A computer generated model of bovine trypsin, a protein dissolving enzyme used in the debridement of wounds. (NIH Photo # 1616)

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NEWS&FEATURES FROM NIH

PORTFOLIO – BURN CARE RESEARCH

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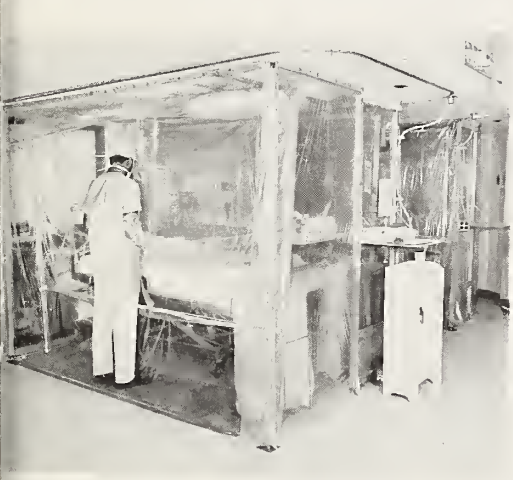

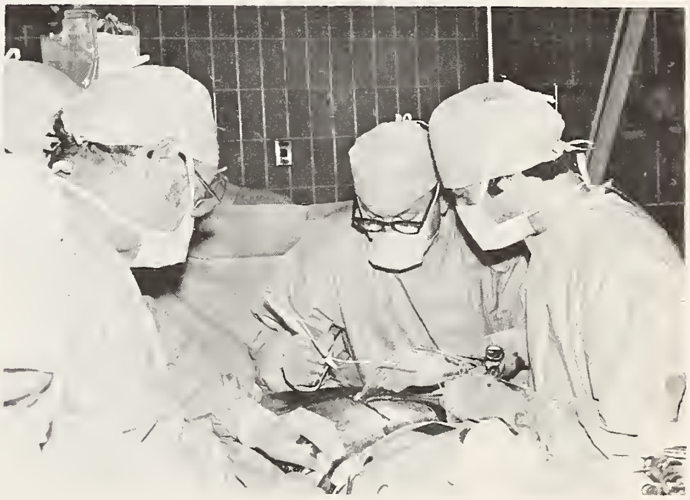

NOVEMBER 1978

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Emilie A. Black, M.D., is Assistant Director for Clinical Research, NIH National Institute of General Medical Sciences. Dr. Black entered the Federal Government in 1968 following 19 years in the private practice of pediatrics. She also served previously in the District of Columbia Department of Public Health. (NIH Photo # BC-1)

PORTFOLIO ON BURN CARE RESEARCH

Introduction by Emilie A. Black, M.D.

A severe burn injury is one of the greatest emotional and physical handicaps known to man. Each year of the approximately 75,000 people who are hospitalized for severe burns (defined as involving 30 percent or greater of the total body surface), more than 30,000 require prolonged intensive care with an average hospital stay of 64 days. Despite the excellence of this care, 10,000 die, making burn injury the third leading cause of accidental death in the U.S. One third of the burn victims are children under 15 years of age,* and generally deaths in males outnumber those in females.

It is surprising that the U.S., which is a leader among the industrialized countries of the world, has the highest death rate and property loss from fire.** The overall economic loss, including medical cost, property loss, and the impact of days lost from work, approaches $1.5 billion per year.

It is evident that the management of severe burns remains a critical problem. There is no vaccine (as for polio myelitis which in its peak year killed 3,100 people) to stop the spread of burn injuries. However, clinican-scientists working in the field of burn medicine are in general agreement that the development of appropriate supportive measures for fluid resuscitation and restoration of caloric balance could lead to greatly reduced mortality. Life threatening infections and pulmonary and renal complications possibly could be prevented.

The goal of the program of the National Institute of General Medical Sciences (NIGMS) is to strengthen the scientific base related to the effects of burn injuries in order to ultimately improve patient care. Support for coordinated basic and clinical investigations related to burns is intended to foster a more rapid application of research advances in the areas of biochemistry, physiology, cell biology, bioengineering, and behavioral sciences. Burn research is directed toward the discovery of better ways to prevent death, mitigate pain, speed recovery of patients, and lessen the extent of disabilities caused by severe burns. A better understanding of the total body response to burn injury is sought including the fundamental aspects of wound healing and biological repair.

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* DHEW Interagency Committee Report, Burn Care, July 1976

** Report of the National Commission on Fire Prevention and Control, America is Burning, May 1973

To accomplish its goals in burn research the NIGMS provides a wide array of support mechanisms. The research center grant is intended to bring about collaboration between basic and clinical scientists. Through the support of research on a group of closely related projects, the center grant seeks to solve significant problems in the field of burn medicine. Several spin-offs have developed from the burn research centers: direct application of successful laboratory findings to patients and the opportunity for active teaching and training programs for residents, nurses, and allied paramedical staff.

Support of individual research projects provides a mechanism for indepth studies of specific aspects of burn pathophysiology such as wound healing, infection, and fluid resuscitation.

In addition, the Institute offers a special research grant for the new investigator (R23), a Research Career Development Award (K04) and Postdoctoral Individual (F32) and Institutional (T32) National Research Service Awards (NRSA) in the area of burn research.

The R23 grant for support for burn research is designed to encourage new investigators to develop their own research projects related to the pathophysiology of severe burn injuries. Its purpose is to help bridge the gap between the research trainee and the independent investigator. A maximum of three years support is offered to the applicant who must devote at least 50 percent of his time to research. The program is intended to provide the initial support for independent research by talented physicians who wish to pursue a research career.

The NIGMS Research Career Development Award (K04) in burn research is a grant for special salary support awarded to an individual with high potential in an active research environment for a biomedical or behavioral research career. It is designed to provide the additional experience which is needed to enable the applicant to launch a career as an independent investigator. Since the rank of associate professor or the successful competition for more than one substantial research grant usually indicates that the candidate has been judged to be an independent investigator, preference in selection of NIGMS awardees will be given to individuals whose achievements at the time of application have not been so recognized. The award is offered for a total of up to five years.

The Postdoctoral Individual National Research Service Awards (F32) are for a total of three years. They are offered to individuals with the M.D. degree who are preparing for careers in clinical research. Ph.D.s who seek competence to apply the knowledge and methods of basic biomedical disciplines to medical problems related to burn injuries may also apply. The Ph.D. usually works in close collaboration with clinical scientists. The M.D. is expected to spend two years in basic sciences laboratories.

The Institutional National Research Service Awards (T32) in burns offer multidisciplinary research training for M.D.s and Ph.D.s to enhance their capability of advancing our knowledge of the body's complex reactions to burn injuries. The supervisory staff should include burn specialists as well as basic scientists. For the M.D., emphasis should be placed on basic training for at least two years withing such departments as physiology, biochemistry, immunology, and microbiology.

Burn Care

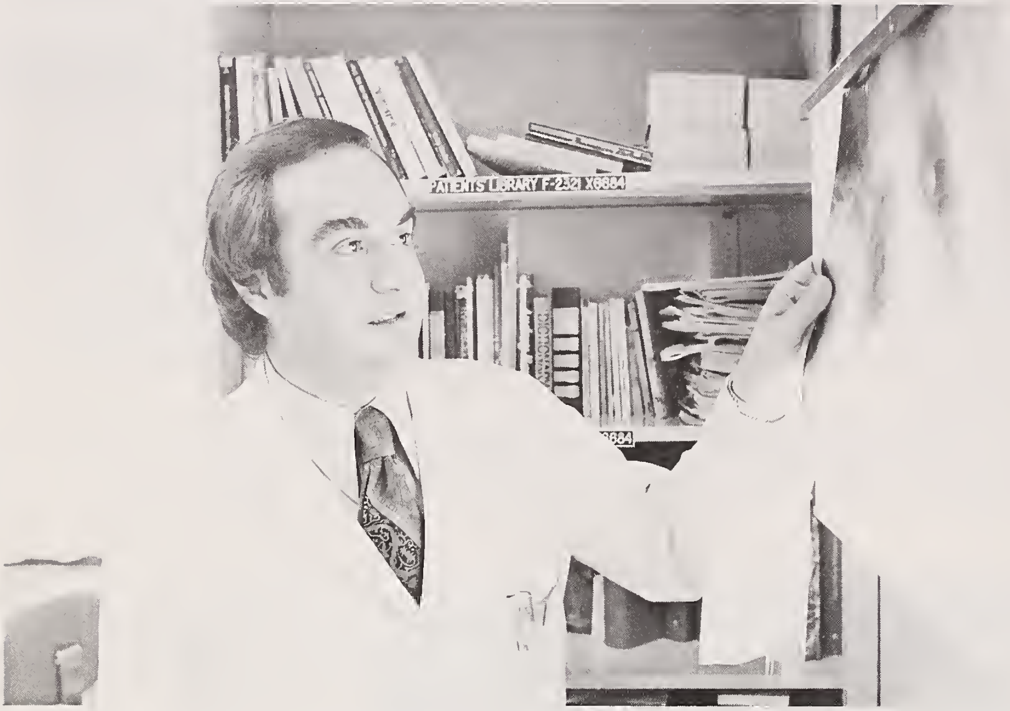
In addition to the granting mechanisms available to investigators, the NIGMS has sponsored a number of conferences related to burn research. These have been in the form of technology assessment and transfer workshops, a consensus development conference, international symposia, and Communications Technology Satellite (CTS) broadcasts on burn research.

During the short time of its existence the burn research program has made marked advances in understanding the extent of burn injury and how best to treat it. Serious burns involving over 90 percent of the total body surface are no longer considered impossible to manage and the patients involved may survive to lead a useful life in society.

The following pages cite some of the accomplishments by NIGMS grantees working in the area of burns.

CORNELL MEDICAL CENTER

DR. P. WILLIAM CURRERI



Dr. P. William Curreri, Professor of Surgery at the Cornell Medical Center and grantee in burn care research from the NIGMS. (NIH Photo # BC-2)

During the past 20 years, mortality and morbidity, as a result of thermal or accidental trauma has been markedly reduced. More rapid transportation of severely injured individuals to burn centers, improved means of fluid resuscitation, better understanding of posttraumatic pulmonary complications, as well as early detection and therapy of septic complications have been instrumental in the improved clinical results.

Statistical analysis of current clinical experience indicates that a 50 percent survival is observed in patients with burns over 60 to 65 percent of their body in the age groups from 0-44 years. A fifty percent survival also is observed in patients with 50 percent burn in the 45-64 age group. The results indicate that there is a 33 to 50 percent improvement in clinical care when compared to similar studies performed in the mid 1960's. In fact, most major burn centers now observe few deaths among their extensively burned young adult population during the first two weeks after burn injury. Thereafter, both mortality and morbidity, as a result of pulmonary dysfunction or wound sepsis are infrequent.

Pulmonary Dysfunction

During the past six years, Dr. P. William Curreri's laboratory has intensively investigated the various physiological insults which induce severe lung dysfunction at various stages following thermal injury. Simultaneously, he and his colleagues have been able to document a striking elevation in the serum concentration of fibrin split products during the first several postburn weeks. Fibrin split products are derived from fibrinogen, the plasma protein which forms the essential portion of a blood clot.

Recent clinical observations have suggested that there exists a cause-and-effect relationship between the appearance of elevated levels of one fibrin split product (fragment D) and the subsequent development of acute respiratory distress syndrome. This relationship has been conclusively demonstrated in nontraumatized, non-anesthetized rabbits. Furthermore, the induction of acute pulmonary failure appears to be mediated through the release of histamine from platelets after induction of elevated fibrin split product levels.

Two alternative therapeutic approaches are potentially available to modify the pathophysiological consequences of increased concentration of fibrin split products. First, it appears that it may be possible to preserve pulmonary function by blocking mediators released from cellular components following induction of elevated fibrin split product levels. Pretreatment with antihistamines in pharmacological doses has been shown to be effective in preventing pulmonary dysfunction in the animal model. Similar agents may prove to be effective prophylactically in burn patients when administered in the immediate posttraumatic period. This clinical study is currently in progress.

A second therapeutic approach would be aimed at pharmacologically altering the production of those specific fibrin split products which appear to induce the greatest toxicity. The development of such a treatment modality is dependent upon the pharmacological toxicity of each fragment released from the degradation of fibrinogen. Current studies are aimed at the clear delineation of the biochemical and pathological mechanisms which result in pulmonary endothelial dysfunction induced by fibrin split products.

Nutrition Therapy

As a result of previous clinical investigation, clinicians throughout the country have become increasingly aware of the importance of nutritional programs when treating the hypermetabolic state of patients with major thermal injury. Death from malnutrition along with cellular and organ dysfunction may often be prevented, if sufficient energy is provided the burned patient. Researchers at Cornell have clearly delineated that patients maintained in prolonged negative energy balance exhibit a "sick cell syndrome" characterized by diminished cellular transport and accumulation of intracellular sodium.

Current investigations are aimed at refining improved treatment modalities which will allow the safe delivery of large caloric intakes. At the same time new means of controlling the hypermetabolic response to burn injury are being investigated, which hopefully will allow more conventional nutritional therapy. Metabolic reserve, often required during temporary periods of stress caused by sepsis or other posttraumatic complications, must be maintained.

Calorie and protein goals in therapeutic dietary programs have been outlined, and extraordinary efforts are required to achieve positive caloric and nitrogen balance. Nevertheless, currently available means of adminstering high concentrations of parenteral carbohydrates through a central vein are not without significant risk in patients with infected burn wounds. The safe reduction of metabolic rate by pharmacological manipulation and the alteration of current treatment methods might permit maintenance of positive energy balance by the more conventional and safer oral and parenteral route.

The major steps in outlining the mechanism of the hypermetabolic response to burn injury during the past few years give promise of finding new and safe means to control therapeutically the metabolic response. It is now relatively well established that the brain's regulatory role in the hypermetabolic response to burn injury is expressed through the neural hormonal pathways involving the hypothalmus and catecholamine production.

Studies during the past few years by Cornell investigators suggest that the hypermetabolic response is initiated by prostglandins, which are known to be released in high concentration from the burn wound. Prostaglandins, hormone-like substances produced by the body from fatty acids, function as regulators and modulators of diverse metabolic processes at the cellular level. Hypermetabolism in an animal model can be diminished by pretreatment with prostaglandin inhibitors, offering hope that a similar treatment may be effective in burn patients.

SHRINERS BURN INSTITUTE, BOSTON

DR. JOHN F. BURKE

Researchers at the Shriners Burn Institute, in collaboration with the Harvard Medical School and the Massachusetts General Hospital are investigating the following five areas:

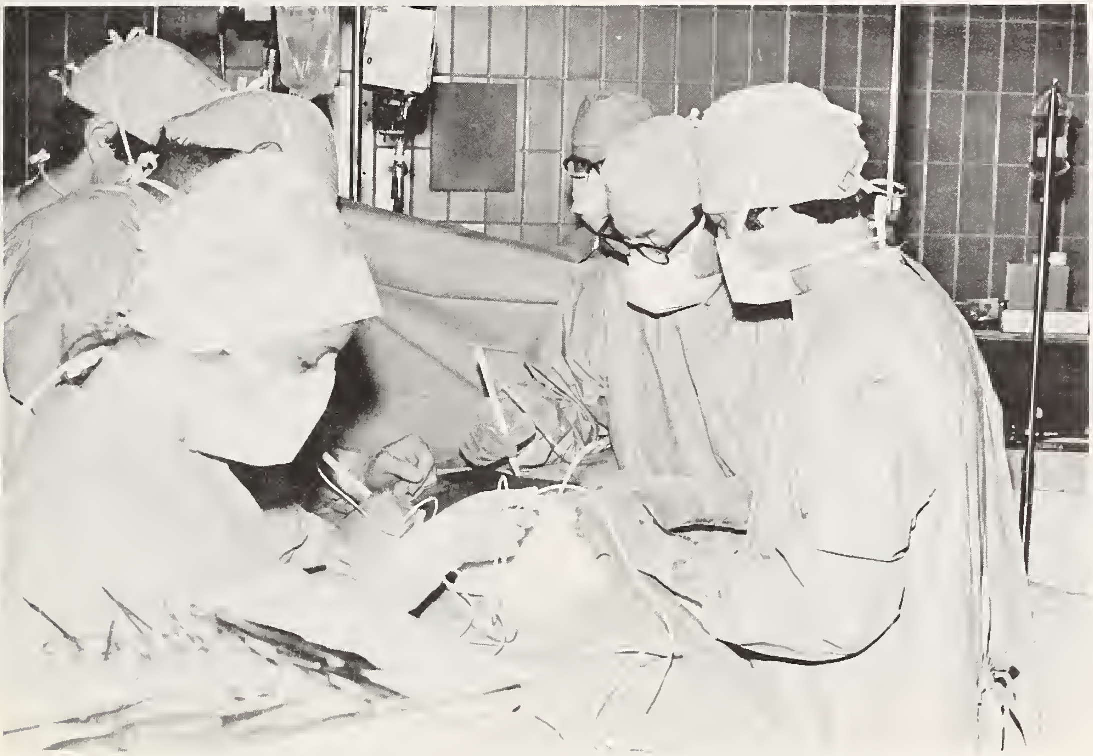
Development of Artificial Skin

Over the last 15 years active research has been carried out in an attempt to identify a synthetic material that would serve satisfactorily as a skin substitute. For the first time a synthetic material has been developed which has proven to be a successful temporary skin substitute in a burned animal.

Investigators at the Shriners Burn Institute, in collaboration with the Mechanical Engineering Department at Massachusetts Institute of Technology, have now devised a composite biomaterial which has some of the biologic and physical properties of skin.

This artificial skin, made from animal tissues, is a composite of carbohydrates and protein fibers derived from cattle. The fibers are reinforced with a second biologic material that protects the fibers from being eroded by the naturally occurring enzymes in tissue. The fiber reinforcement makes the material strong and, when it is in place, covering a burned area, it prevents fluid loss and infection, two of the most serious complications of severe burns.

The material does not produce inflammation or irritation to the tissue, stimulate antibody formation, nor act as a foreign body in the tissue. A physiologic interation takes place between the burned tissue and the synthetic covering. Normal fibroblasts from the burned animals, as well as normal blood vessels, have been induced to grow into the skin graft material so that, after a few days, the synthetic material which is populated with the cells of the injured animal so that it is then not completely foreign. Human studies are planned in the near future.



Primary Excision and Immediate Wound Closure

It has always been recognized that survival and recovery from a burn injury are dependent on the removal of the skin killed by the burn (eschar) and on the repair of the resulting open wound. Until recently the eschar was allowed to separate spontaneously over a period of three to four weeks. This delay created a life-threatening condition in the patient. Methods have now been developed to satisfactorily stabilize the patient so that extensive surgical procedures such as removing the eschar and replacing it with skin grafts can be completed in the first few days following injury.

The first successful use of this early excision and prompt wound closure as a routine method for burn care was developed over the last seven years. The results have demonstrated that this treatment method not only reduces the mortality but also improves the patient's ability to function. Early excision and wound closure reduces the time necessary for treatment to about half of that required by previous methods.

Hypotensive Anesthesia

The amount of blood loss during primary excision of burn eschar has made this procedure a complicated and difficult procedure. The development of hypotensive anethesia in the burn patient has provided a significant reduction in the amount of blood lost during the operation and has greatly improved the effectiveness and safety of early excisional therapy.

Hypotensive anesthetic technique permits the deliberate reduction of the patient's blood pressure at any point during the surgical operation when blood loss is marked. Blood pressure can be restored back to normo-tensive levels in less than a minute's time. Accurate blood pressure control is achieved by the use of a potent drug, sodium nitroprusside, which dilates the small blood vessels of the body, thus reducing the resistance to flow and lowering the blood pressure.

Sensitive control of blood pressure reduction to levels where blood loss is markedly reduced but where accurate tissue perfusion is maintained is achieved through the monitoring of the patient's central arterial pressure and cardiac activity. Electronic devices continuously read out the pressure on an oscilloscope for the anesthesiologist and the surgeon to see. Using this method of anesthesia, surgery has been made safer and treatment of the burn patient more effective.

Bacteria Controlled Nursing Unit

Bacterial infection is a constant and serious danger to the burned patient. Immediately after the injury itself the loss of skin prevents exclusion of bacteria from the body. Infection, despite the extensive use of antibiotics, continues to be a frequent cause of death or serious complication.

In the burned patient who is so susceptible to bacterial infection, and in whom treatment is extremely difficult, prevention of such infection is of the utmost importance. Infection of the wound can be prevented if bacteria are excluded from the patient's surroundings. The Bacteria Controlled Nursing Unit, which provides a protective environment for the burned patient, is highly effective in keeping bacteria from the patient's surroundings out of the burn wound.

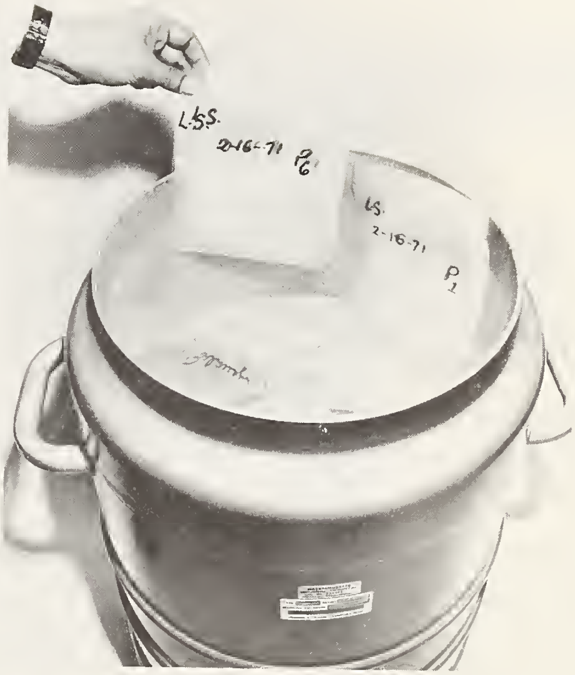
This isolation is accomplished by the use of see-through curtain walls and a piston-like down-flow of bacteria-free air that constantly washes over the patient. In addition to protecting the patient from bacterial contamination, the protective environment provides the temperature and humidity control exactly suited to the patient's needs. The medical and nursing staff who perform all treatment from outside the protective environment itself can work at ordinary, comfortable room temperature.

Immunosuppression and Temporary Skin Transplantation

Survival following a deep burn which covers 80 percent or more of the body surface has only recently been possible. Success in treating this group of patients is largely related to the development of a satisfactory treatment to prevent the rejection of skin grafts using skin from other individuals for periods of two months or more.

A patient with an extensive burn is under serious risk until all dead tissue is removed and the wound closed with living skin. This living skin must eventually come from the burned patient himself as a thin layer from the remaining unburned skin in split thickness skin grafts.

(A)



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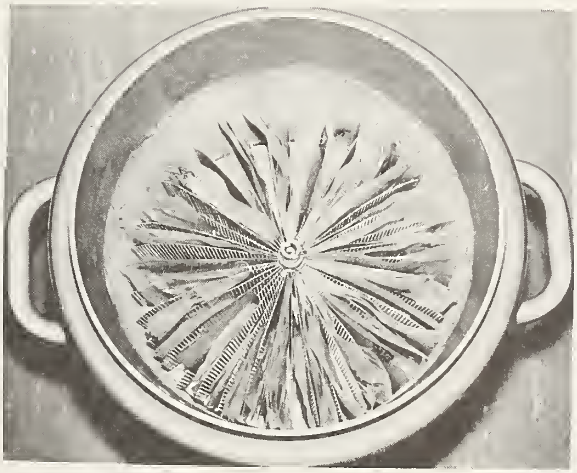


(C)

(A) Skin grafts being prepared for storage in the "skin bank" (NIH Photo # BC-3)

(B) The grafts being frozen in sealed plastic envelopes (NIH Photo # BC-4)

(C) A "skin bank" repository in the deep freeze. (NIH Photo # BC-5)

However, in a serious burn the area of unburned skin is often not large enough to supply the split thickness grafts needed for closure. This problem can be temporarily solved by borrowing skin (allograft) from other people.

Using a typing system similar to that used to type blood, a skin donor, usually a family member, is selected. The ability to use allograft skin has been dramatically improved by the development of reliable and efficient methods of skin banking. The first operational skin bank was opened at Boston Shriners Burn Institute in 1969.

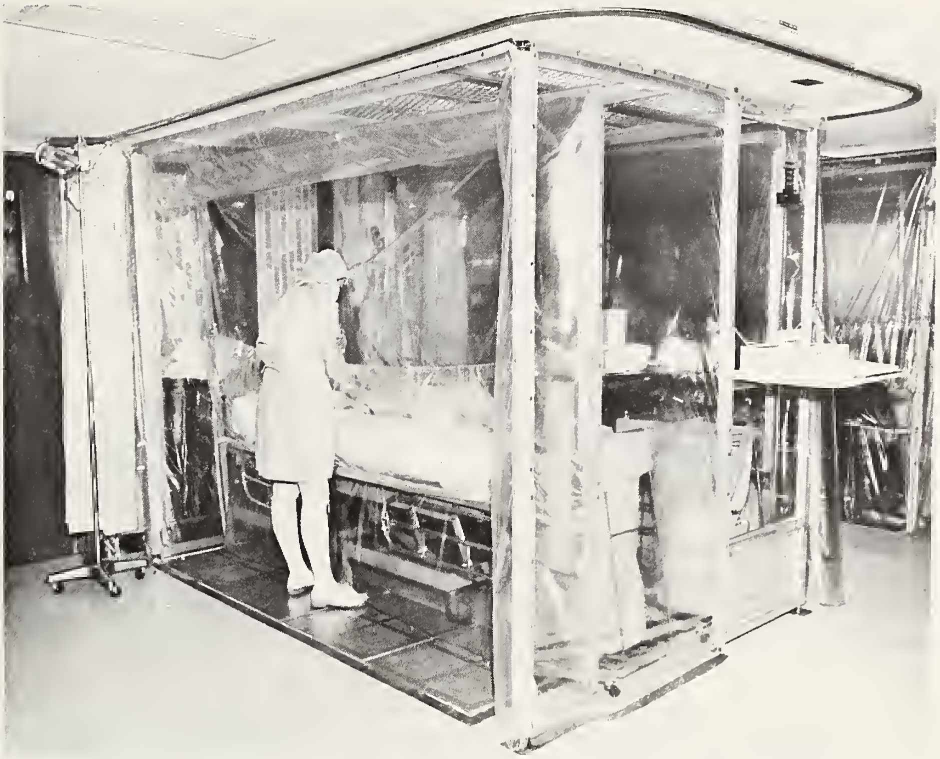
The donor skin can be borrowed from the bank to temporarily replace the burned skin for periods long enough to allow repeated harvesting of the small area of the unburned skin as it regenerates.

In the first 10 days post-injury, the dead tissue is completely removed in up to five operations. During the first operation the portion of dead tissue removed is replaced with skin harvested from the unburned skin of the patient. While this donor site regenerates for a second cropping, the subsequent operations remove the remaining portion of the burned skin which is replaced by split thickness skin obtained from the most suitable donor.

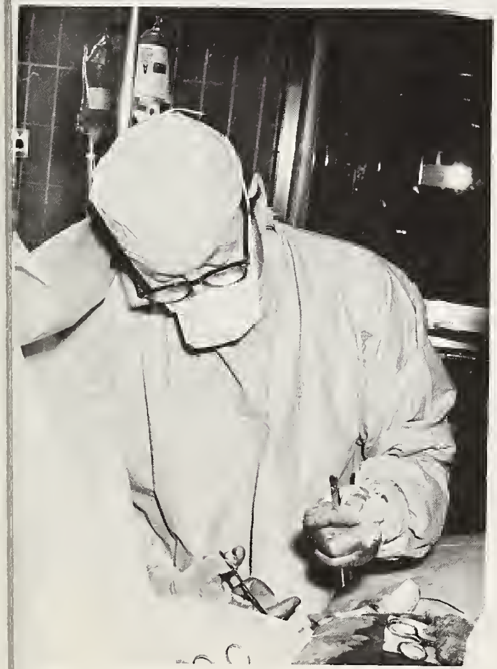
The rejection of this "non-self" skin, which would ordinarily occur in about two weeks, is prevented by a treatment called immunosuppression which prevents the patient from rejecting the foreign tissue. Rejction is prevented by destroying the cells, the T-lymphocytes, which normally recognize and destroy foreign cells or tissue. This is done by using a specially prepared antibody to the T-lymphocytes themselves.

The dose of the administered antibody is of great importance. If too little antibody is given the T-cells will persist and rejection of the skin graft will occur. If more antibody is given than needed, the patient's defenses against bacterial invasion will be impaired and infection will result.

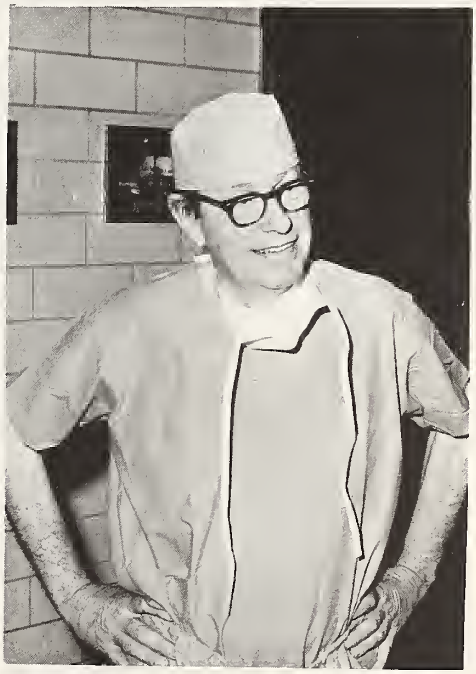
Regulation of the dose of antibody, is therefore, carefully carried out by a diagnostic test called a rosette count which uses sheep red blood cells that naturally stick to and identify T-lymphocytes. With the use of specific doses of antibody to T-lymphocytes, skin graft rejection is prevented and about two-thirds of the patients who were massively burned have survived and have returned to normal life.



A plastic isolation tent in the bacteria controlled Nursing Unit. (NIH Photo # BC-6)



Dr. John F. Burke performs primary excisional surgery. Dr. Burke is an NIGMS grantee. (NIH Photo # BC-7)



Dr. Burke is Chief of Staff at the Shriners Burn Institute and Professor of Surgery, Harvard Medical School. (NIH Photo # BC-8)

SAN FRANCISCO GENERAL HOSPITAL

DR. DONALD D. TRUNKEY

Burn research at the San Francisco Trauma Center has been directed toward finding the causes of immune depression following thermal injury. When the immune system is shocked, the burn patient can be left defenseless against a wide variety of infectious organisms.

Body cells which play a major role in the immune response are the lymphocytes and macrophages. The major types of lymphocytes are the thymus-derived T-cells, and the bone marrow-derived B-cells. The macrophages are large mononuclear cells which act as accessory to the T-cells.

Mature B-cells are responsible for the manufacturing of antibodies which circulate in the blood or other body fluids. Such antibodies, in turn, respond to antigens found on the surface of most viruses and bacteria, preventing spread of infection.

Initial investigations by the San Francisco researchers, using a combined clinical and laboratory approach, found that the activity of the B-cells in producing antibody was unaffected by burn injury. This was not the case, however, in patients who were nutritionally depleted.

T-cells are produced in the thymus, an organ located in the upper front part of the chest just under the breast bone. Complex interaction between the macrophages and the T-cells provide cellular immunity and are very important in protecting a person from certain micro-organisms such as fungi and molds. Macrophages and T-cells are also largely responsible for the rejection of tissue transplants and for skin reactions to poison ivy and other allergens.

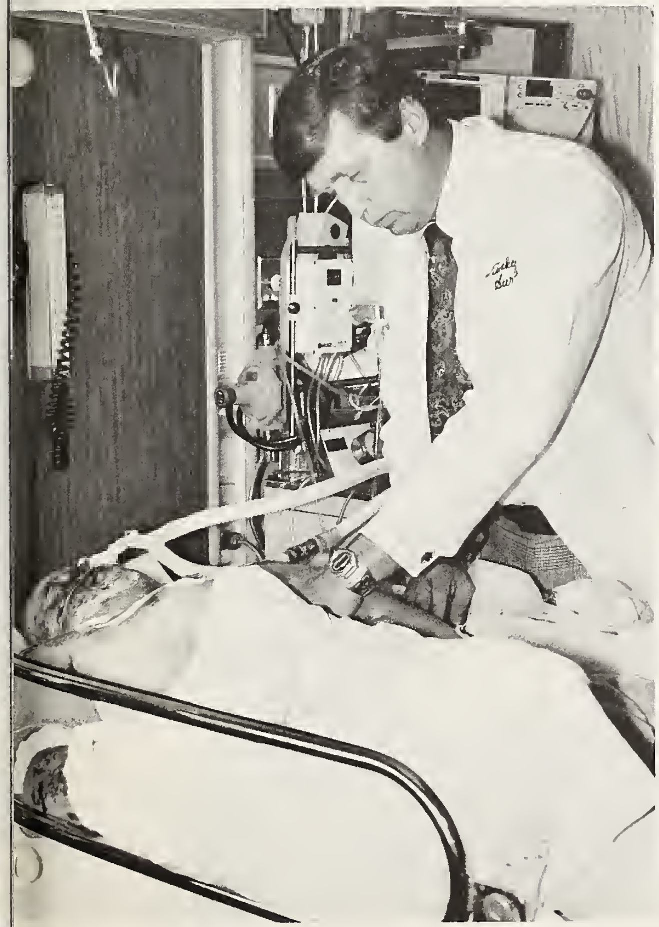
Dr. Donald D. Trunkey performs laboratory tests to determine T-cell activity with Dr. Carol Miller, staff immunologist at the Trauma Center. (NIH Photo # BC-9)

The three cell types form a "network" which regulates the production of antibodies and of the other systemic defensive responses to "alien" invaders. Balancing the activity of this defensive network in the normal person is that of the suppressor T-cells, which help regulate the immune response. Auto-immune diseases, such as arthritis, are believed to result from the failure of the suppressor system to function adequately, permitting the body to literally become allergic to itself and destroy certain of its own tissues.

Massive burn injury seems to cause the opposite reaction to take place. The suppressor T-cell system becomes hyperactive, throwing the defensive network out of balance.

It has been shown in mice that the suppressor T-cells can modulate the accessory macrophages to inhibit rather than aid in the T-cells' immune response. Removal of the suppressor T-cells and replacement by normal T-cells restored the immune response in the mice.

An increase in suppressor T-cells has been identified in extensively burned patients. Although it is not found in all patients, its presence is associated with a 75 percent mortality due to infection.



Dr. Trunkey is Associate Professor of Surgery at San Francisco General Hospital and an NIGMS grantee. (NIH Photo # BC-10)

The San Francisco researchers are currently investigating the close but little understood relation between T-cell function and macrophage function. In thermal injury the macrophages are engaged in engulfing debris thrown off by the burn wound. This clean-up response may distort the macrophages' ability to communicate with the T-cells, leading to the overstimulation of suppressor T-cell activity and leaving the burn victim susceptible to infection.

At present the approach taken by the San Francisco researchers is to determine which immune cell system may be out of order to identify the patients at risk. For those burn patients found at risk, antibiotics are given in prophylactic doses.

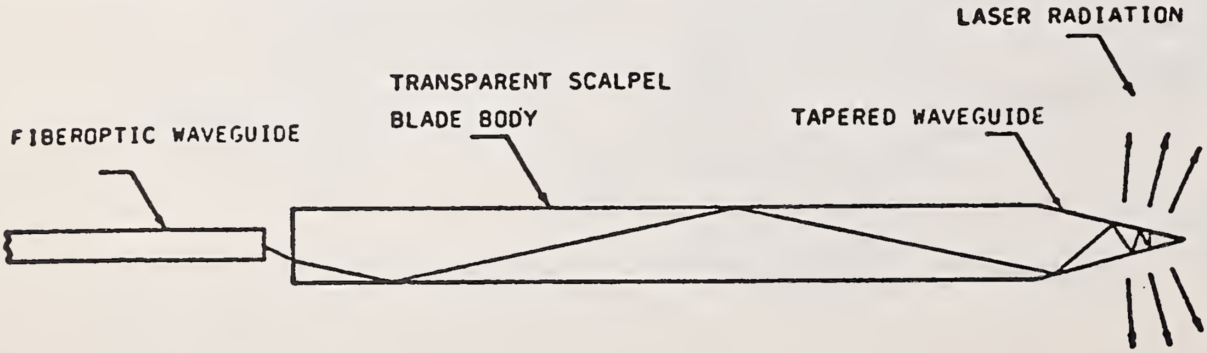
Ultimately the San Francisco researchers hope to manipulate pharmacologically the immune system in order to restore the necessary balance. Such manipulation could take the form of heparin administration to reduce the amount of debris thrown off by the injury, or thymosin dosage to stimulate the production of T-cells. Experimental work is currently being done in animals to find the most effective and least hazardous treatment.

UNIVERSITY OF WASHINGTON SCHOOL OF MEDICINE DR. C. JAMES CARRICO

Advances in several areas of research at the University of Washington School of Medicine are leading to significant improvements in patient care. Among these are the following five developments:

Laser Scalpel

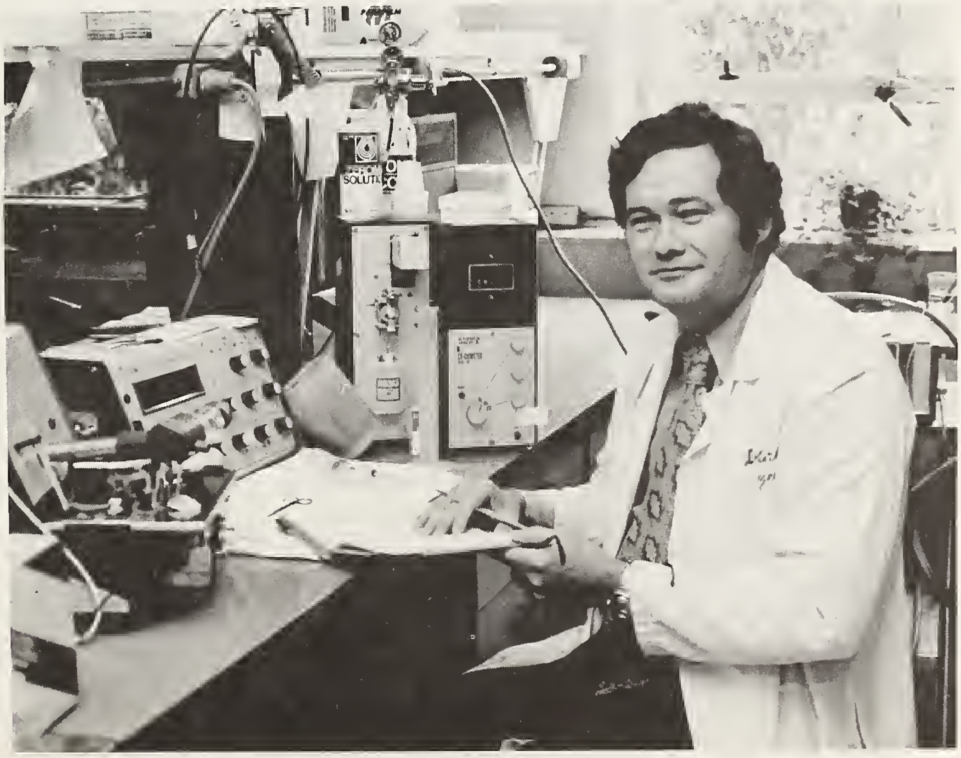
A new type of laser scalpel has been developed under the leadership of Dr. David Auth, Associate Professor of Bioengineering and Dr. David Heimbach, Associate Professor of Surgery. The scalpel uses high power argon laser radiation transported via a single low loss optical fiber into and through a transparent sharp knife. Laser radiation can be flexibly coupled from a laser source through a fiberoptic waveguide, and then coupled into the transparent scalpel blade. The radiation is trapped within the transparent blade by the critical angle of internal reflection for the particular dielectric material (quartz or sapphire) comprising the blade. The laser radiation forms from the input edge toward the tapered scalpel edge defining a sharp mechanical knife. The laser light reflected out at the tapered zone is available for hemostasis of vessels proximal to the cutting edge of the blade. Thus, as an incision is made, the blood vessels are pressed shut and fused with a cauterizing dose of laser radiation at the margin of the incision.



Green argon laser radiation is used because it is available in high power and because it is selectively absorbed by the red color of hemoglobin. The selective absorption by red blood cells permits preferential coagulation of blood with minimal damage to surrounding white tissue. The hemostatic properties of the laser are utilized in conjunction with a sharp mechanical knife.

Several models of the "laser blade" have been developed over the past several years. Both quartz and sapphire material have been used for the transparent blade and many ways of coupling the laser light from the fiberoptic wave guide into the transparent blade have been investigated. In addition, several geometric configurations for the blade have been developed. The blades are sufficiently sharp to permit cutting of tissue without laser radiation being present. In fact, the laser radiation appears to improve the blade's cutting efficiency for tissue.

Bleeding in animals has been investigated to compare the laser blade with the cold knife and the electro-cautery knife. The blood loss with the laser was extremely small, contrasted with a very large and profuse blood loss with the cold steel scalpel. On the average, the laser blade took nearly the same time to debride burn wounds as did the electric cautery knife but the blood loss was reduced by a factor of approximately threefold. These results show that a dramatic improvement is possible with the laser blade as compared to the standard surgical blade or to the electric knife, even when the electric knife is used in a careful hemostatic manner. Histological evaluation of tissue destruction



Dr. C. James Carrico is Professor of Surgery at the University of Washington, Seattle and a grantee of the NIGMS. (NIH Photo # BC-11) has shown that the depth of necrosis with the laser blade is approximately one-third that which is seen with the electric knife.

This new technique of laser surgery appears to hold great promise as a means of performing surgery in heavily vascularized regions with precise control and tactile sensation. It is being used in selected burn patients.

Modified Whole Blood Transfusions

Studies conducted by the University of Washington researchers in conjunction with the Puget Sound Blood Center in Seattle, Washington have resulted in increas understanding of the physiologic effects of massive transfusions and have led to significant changes in transfusion practices. The sometimes massive amounts of blood required for the treatment of injured patients and the evolution of early excisional therapy of burns has made this knowledge of the requirements for transfused elements event more important.

The Blood Center has developed and adapted techniques for the removal and storage of platelets from fresh blood and for the removal of Factor VIII (anti-hemophiliac globulin) for use in hemophilia and other clotting abnormalities. The blood available is thus "modified whole blood" which has all of the usual components other than Factor VIII and platelets.

An initial study was conducted to determine the reliability and safety of using this modified whole blood for replacement of massive blood loss. The results of this investigation confirmed the fact that injured and stressed patients produce excess amounts of Factor VIII and thus no adverse consequences resulted from administration of blood deficient in Factor VIII.

Thrombocytopenia (or platelet depletion) was found in injured patients following administration of large amounts of modified whole blood; however, this same problem is described after massive transfusion with any sort of banked blood. Thus, modified whole blood appears to be a safe and advantageous product for administration to patients with massive blood loss.

The study further showed that abnormal bleeding (bleeding due to abnormal coagulation rather than to direct vessel injuries) was very low in these patients. Studies are now underway to determine if platelets should be given at a predetermined point during massive transfusion of patients or platelet administration should be delayed until signs of abnormal bleeding occur.

Sodium Content Signals Infection

Overwhelming infection remains a major problem in burned and traumatized patients. The ability to diagnose the presence of systemic infection early depends on clinical signs. Culturing organsims form the blood stream is not always reliable, and the growth of organisms is not seen until hours or days after the start of the bacteremia.

Preliminary studies in the Trauma Unit have suggested that alterations in the function of the red cell membrane cause the sodium content of the cells to rise. Although this change is always found in nutritionally depleted patients, it is also found in patients with adequate nutrition. Should the current animal studies confirm these findings, this sodium shift is expected to represent a valuable tool in diagnosis and early treatment of overwhelming infection.

Other studies along the same line include attempts to identify antibodies to gram negative organisms which usually cause such infections. These antibodies may be used as an early indicator of significant systemic infection.

Doppler Principle Measures Cardiac Function

In using fluid therapy in burned patients and other injured patients it is essential to measure the cardiac output and its response to therapy. Current measuring techniques involve invasion of the vascular tree and frequently require the always risky insertion of a catheter into the pulmonary artery. In conjunction with the department of bioengineering, an ultrasound device using the Doppler principle is being evaluated for the measurement of the cardiac output.

This device has proved accurate in animals and in a small group of patients within the Intensive Care Unit. Its reliability under extreme conditions such as those in patients requiring special breathing assistance (positive end expiratory pressure) is being evaluated. The fact that this instrument is non-invasive and carries very little risk will permit the use of such sophisticated monitoring in a much broader spectrum of patients.

IVERSITY OF TEXAS
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DR. CHARLES BAXTER

Severe burn injury results in a unique type of "shock" which is characterized by the initial translocation of tremendous quantities of body fluid and a series of body-wide pathophysiologic events which challenge both the immediate and ultimate survival of the patient. Significant progress has been made in defining the quantity, type and timing of fluid replacement necessary to restore circulatory adequacy and thus minimize the early deaths resulting from inadequate resuscitation, once the leading cause of mortality among burn victims.

Studies of the mechanisms responsible for body fluid losses have been undertaken at the University of Texas Health Science Center at Dallas. These have yielded unexpected results. It has been found that, immediately after injury, sodium and water were translocated into normal skeletal muscle cells far removed from the injury site, as well as being lost into the tissues in the area of injury.

The pathogenesis of burn wound edema has been studied and found to arise principally as a result of abnormal extravascular clotting within the wounded area. Semifluid gels of fibrinogen (blood-clotting protein) degradation products, found in great quantity both in and beneath the area of injury, progressively obliterate the lymphatic and venous drainage. These fibrin "splits" effectively block the rapid mobilization of fluid entering the wounded area.

Resorption of these clotting fractions were found in the systemic circulation and have now been implicated in the abnormally fast clotting time of the blood. They may also be involved in several important pathologic processes which include a factor responsible for decreasing the pumping action of the heart, increases in lung capillary permeability, and perhaps several more physiologic and biochemical events vital to normal organ function.

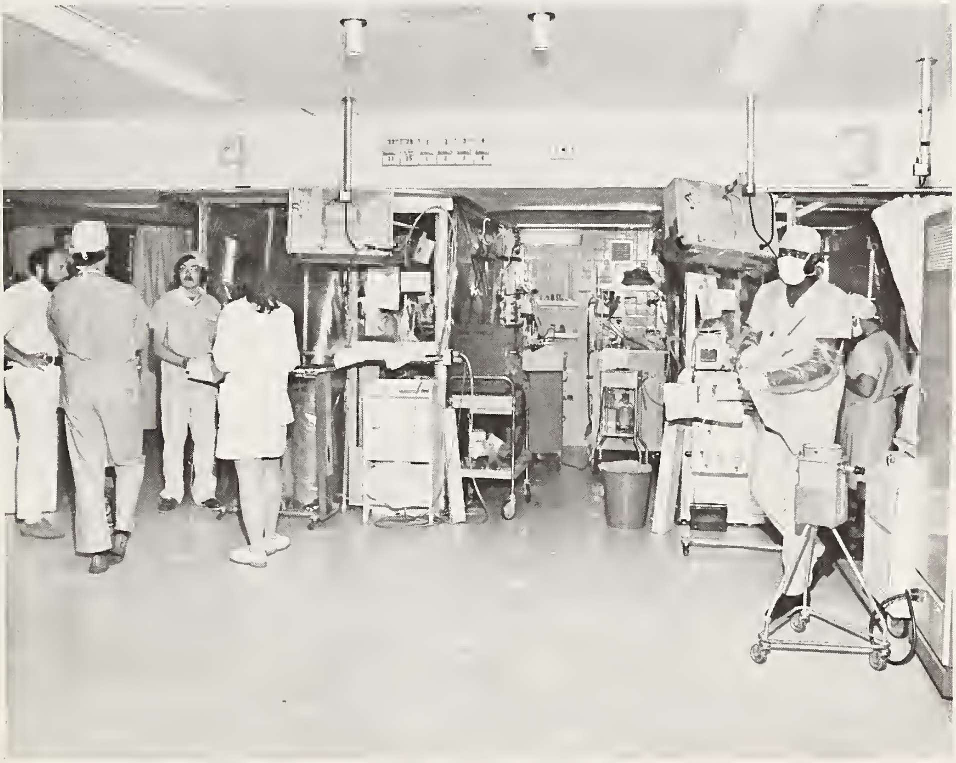
Study of the many significant systemic problems threatening early survival in burn victims has yielded new information important in treatment. Foremost has been the redefining of the mechanism of the early and severe anemia from increased red blood cell (erythrocyte) destruction during the first weeks after injury. This destruction was once thought to result from heat damage to the erythrocytes at the time of injury.
Crossover studies in patients and normal volunteers have shown that abnormal cell wall morphology can be corrected by placing the cells from the burn patient in normal plasma from an unburned recipient (^{51}Cr labeled RBC cross transfer). This information furnished several clues to the basic biochemical derangements in the cell wall that are currently being pursued. This may result in preventive therapy which may decrease dramatically the number of transfusions necessary for burn care.

Dr. Charles Baxter is Professor of Surgery at the University of Texas Health Science Center at Dallas and an NIGMS burn care research grantee. (NIH Photo # BC-12)

It has been noted that cardiac function is often significantly compromised in the first days following thermal injury by a circulating myocardium depressant factor. Additional studies of the heart following this period have found it to be hypercontractile, exhibiting a work load comparable to that of a competing athlete. Both the cause and treatment of this contractility are being vigorously pursued since it is likely that this physiologic abnormality weighs heavily on the ultimate outcome of many burn victims.

Repetitive studies of cardiac output ejection fraction and muscle fiber length are being conducted by noninvasive radioisotope myocardial imaging in both clinical and experimental subjects. Several other lines of investigation are being undertaken to better understand and control this devastating abnormality. Clinically, the changes in the body fluid spaces, including blood volume, metabolic rate, anemia and other factors are being documented as a basis for employing pharmacologic therapy.

The past decade of studies have produced a more optimal resuscitation treatment regimen and proceeded to establish a more realistic pathologic description of the burn illness. Research has now entered into the phase of biochemical definition of the observed pathophysiologic events. This may result in new modes of beneficial therapy.



ST. JOHN'S MERCY MEDICAL CENTER DR. WILLIAM W. MONAFO

Dr. William W. Monafo (left) consults with two of his staff. Dr. Monafo is chairman of the department of surgery at St. John's Mercy Hospital, St. Louis and an NIGMS grantee. (NIH Photo # BC-13)

Research at St. John's Mercy Medical Center in St. Louis, Missouri has focused on three major areas: burn shock and its treatment; control of the microbial flora in the wound with topical agents; and the hypermetabolism that occurs after thermal injury.

Previous work at St. John's has shown that burn injury induces a major extravascular sodium deficit which must be corrected to prevent death. Moreover, the presence of associated lung injury significantly increases the sodium requirements necessary for resuscitation. It has been demonstrated at this institution that the volumes of sodium-containing fluids necessary for resuscitation (both experimentally and clinically) can be decreased by 30-50 percent by using balanced hypertonic sodium solutions.

More recently, the effects of the histamine H_2 receptor blockade in burn shock have been under study. The preliminary evidence is that the sodium and water flux into the injured tissue can be significantly reduced by H_2 receptor blockade, thus concomitantly reducing the water and sodium requirement for resuscitation.

In the area of topical antisepsis, significantly improved clinical results have occurred by the incorporation of the antibacterial salt, cerium nitrate, int the already widely used silver sulfadiazine cream. Gram-negative bacterial burn wound infections have occurred much less frequently in severely burned patients when this agent is used prophylactically, resulting in a lower mortality rate.

Using a clinical environmental chamber, the investigators are presently studying the effects of thermal injuries of varying extents and depths on the metabolic rate and on the mechanisms of heat loss. Oxygen consumption, wet heat loss, and skin and wound temperatures are being monitored under different ambient conditions in the pathogenesis of burn hypermetabolism, and at varying times after injury. The goal is to further elucidate the role of increased water vapor loss that occurs through burned skin.

In extensively burned patients exercise tolerance is also being quantitated at varying times after their convalescence in the environmental chamber. Extensive areas of grafted skin seriously impair the ability of the body to dissipate a sudden heat load. Preliminary evidence, however, indicates that, with time, adaptation and/or conditioning results in lessening of the hyperthermia that attends exercise. These data will be important in determining the degree of permanent disability resulting from burn injury.

Dr. Charles Baxter at the Dallas Health Science Center evaluates a report with a laboratory assistant. Surrounding them is the complex instrumentation used in assessing burn patient status. *(NIH Photo #BC-15)*

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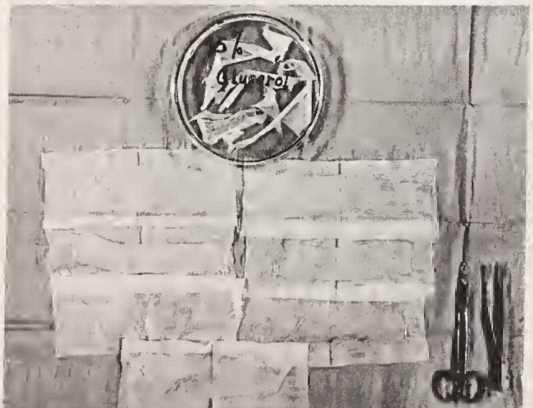

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PORTFOLIO - SKIN DISEASES

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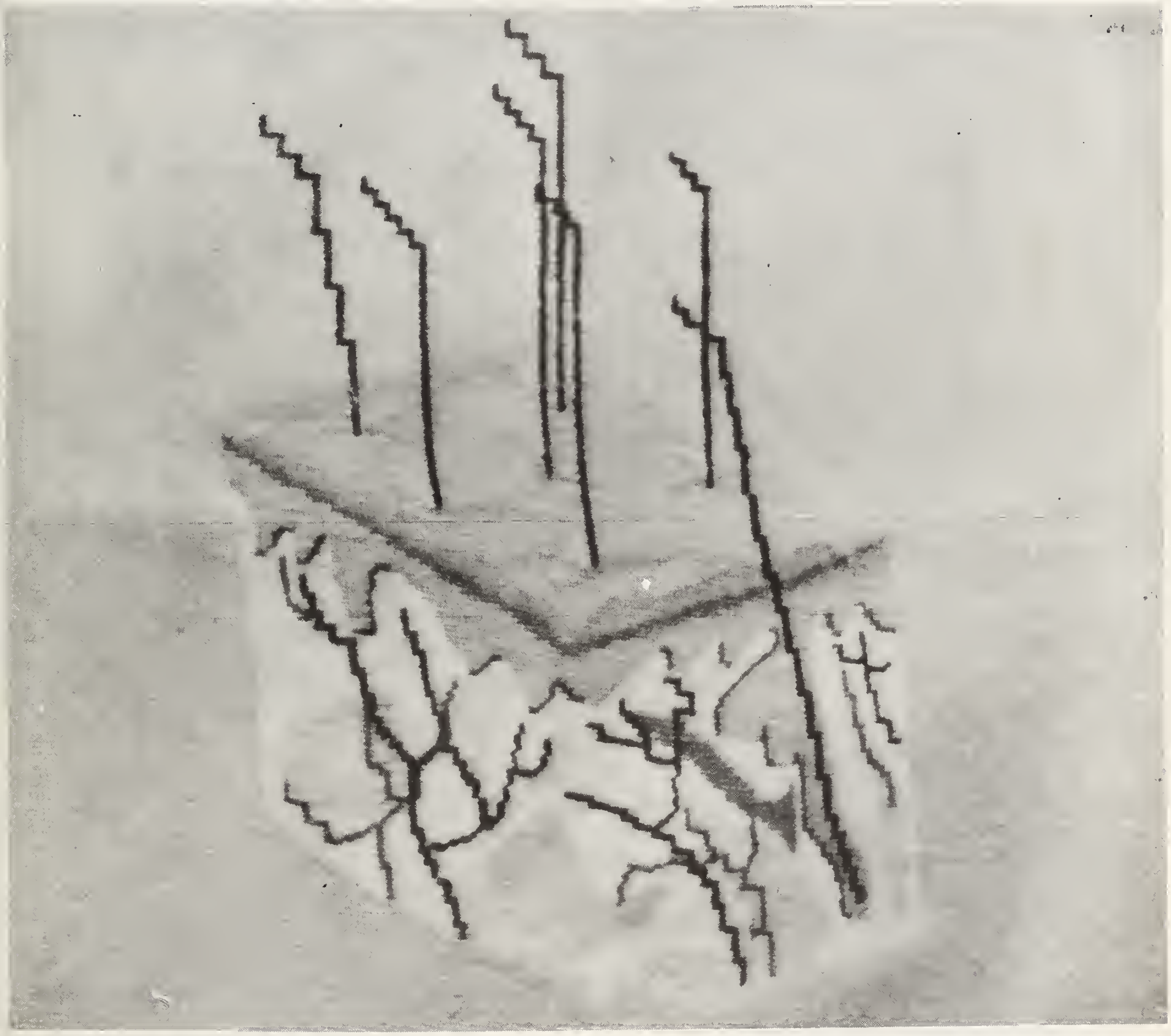

Needlepoint by Leslie M. Miller depicting a cross-section of human skin.

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NIH Portfolio of Skin Diseases--Part Two

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PORTFOLIO OF SKIN DISEASES: INTRODUCTION

The National Center for Health Statistics published in January 1977 a report on the prevalence of dermatological disease among persons 1 to 74 years of age in the United States. This report provided data from a health and nutrition examination survey on the incidence of dermatologic disease in our society. Nearly one-third, or an estimated 60.6 million, have one or more significant skin conditions, and of these affected individuals 3.4 percent, or an estimated 2.1 million persons, have a disability severe enough to be a handicap to gainful employment or housework. In addition, it is estimated that diseases of the skin and subcutaneous tissue account for two percent of the morbidity costs resulting from loss of productive labor for gainfully employed individuals, an economic loss in 1972 estimated at $355 million.

Federal support of basic research into diseases of the skin is provided mainly through the Extramural Programs of the National Institute of Arthritis, Metabolism, and Digestive Diseases (NIAMDD) of the National Institutes of Health. While a number of dermatologic diseases today are still fatal, the seriousness of most dermatologic disorders is due to the distressing visibilit of their anatomical location; they can be totally disabling and disfiguring, destroying lives without actually being lethal. Because of these aspects, the medical, psychological, social and economic impacts of cutaneous diseases are considerable.

(more)

INTRODUCTION (Continued)

The rapid expansion of Dermatology departments in the last twenty years has been outstripped by the explosive expansion of information within that specialty and in related areas of medical research. In response to public and Congressional interest NIAMDD funding of research and research training in cutaneous biology and dermatology has likewise increased. Currently support is being provided for research in psoriasis, acne, atopic dermatitis, blistering diseases (pemphigus, phemphigoid), lupus erythematosus, pigmentary disorders (vitiligo), scleroderma and others. At a more basic level financial aid is being provided for studies in anatomy, biochemistry, physiology, histochemistry and ultrastructure of the skin and its appendages. This includes studies of the effects of aging, radiation and ultraviolet on skin, hair and nails and their structure and function, studies on the process of keratinization, sweat gland function and collagen disorders. Cutaneous microcirculation immunology and metabolism are beginning to receive more attention.

This portfolio illustrates work being performed by some of the scientists who are conducting NIH-supported research in cutaneous biology and on specific skin disorders.

This portfolio was prepared by Laurence H. Miller, M.D., Dermatology Program Director, Extramural Programs, National Institute of Arthritis, Metabolism, and Digestive Diseases. He was assisted by Loraine J. McDonnell.

Shown in this Portfolio are:

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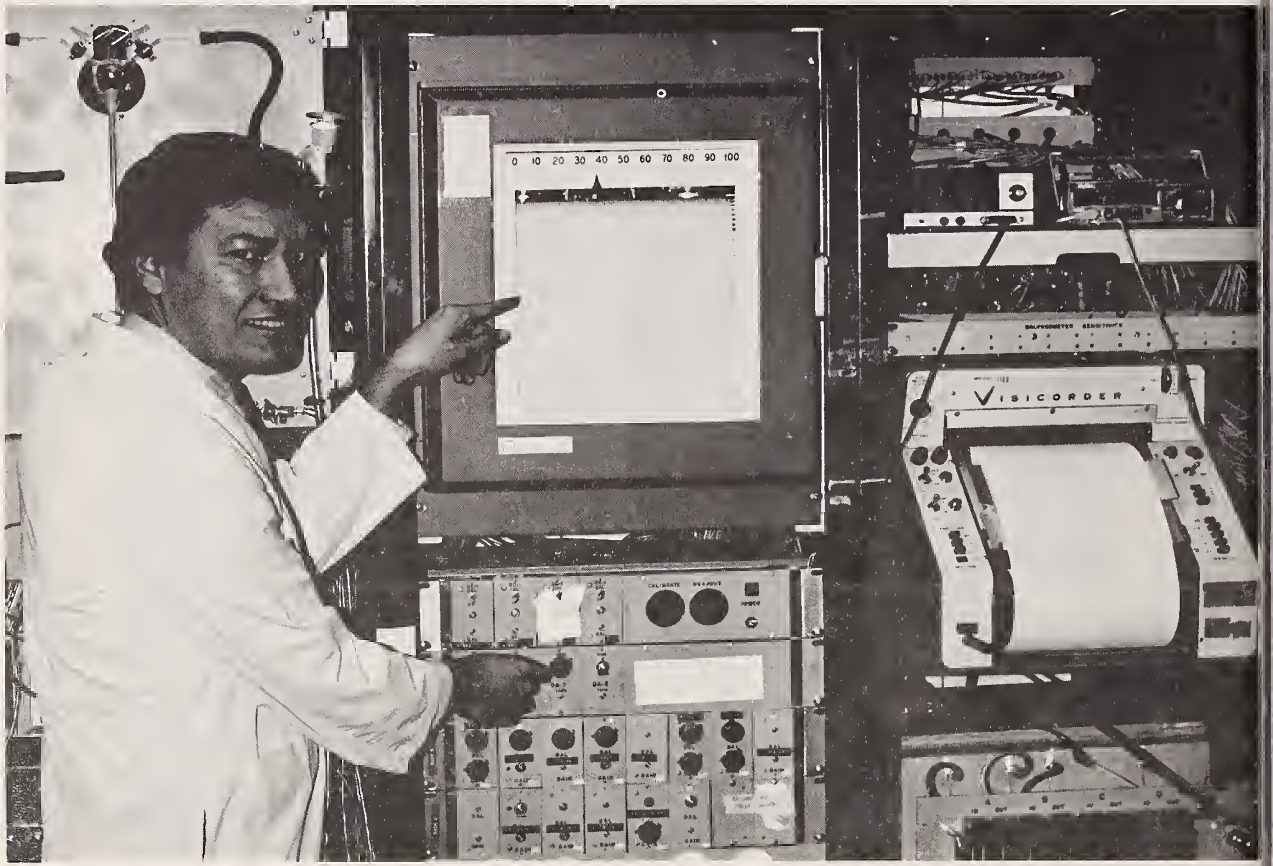
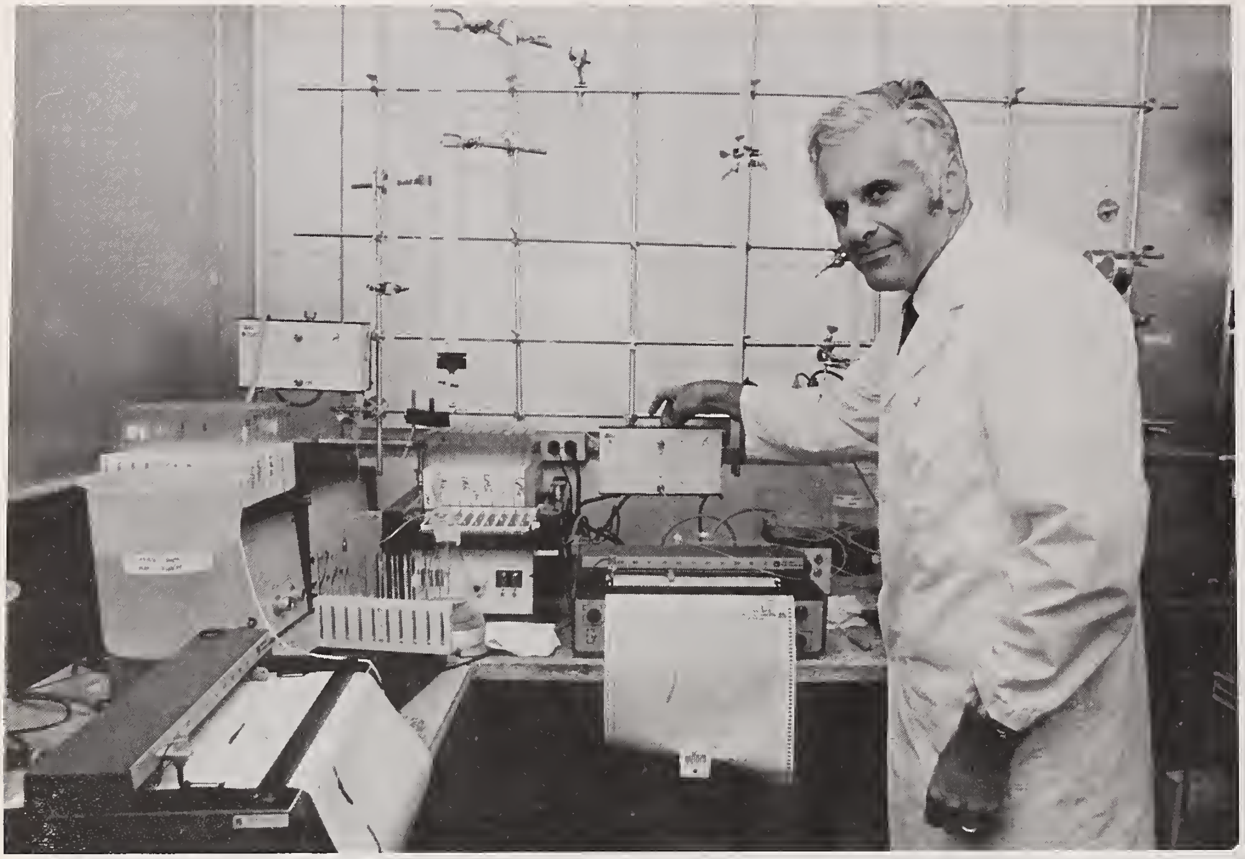
Gopal M. Bhatnagar, Ph.D., is Assistant Professor of Dermatology at The Johns Hopkins University, School of Medicine. In his laboratory Dr. Bhatnagar is studying the role of contractile proteins in normal epidermis and in clinical situations associated with rapid epidermal turnover such as psoriasis, cutaneous malignancy or wound healing. Dr. Bhatnagar is setting up a preparative gel electrophoresis unit which is being used for separation of these contractile proteins. His research is being supported by the NIAMDD.



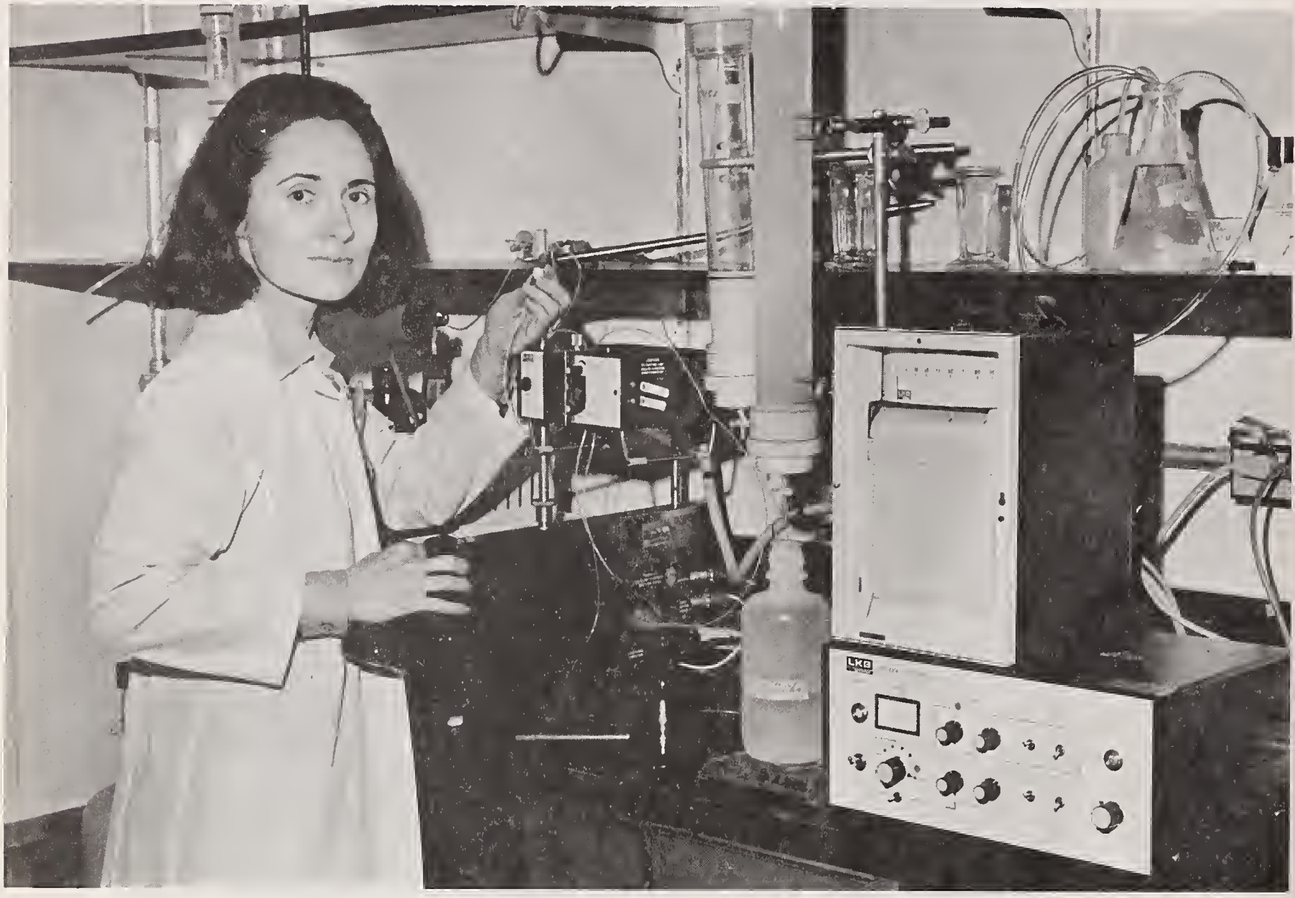
Within the Physiology Section of the Medical Sciences Program at the Indiana University School of Medicine, Dr. Reynaldo S. Elizondo is the principal investigator of an NIAMDD grant. The objective of his particular project is to conduct a series of studies designed to characterize and quantitate the thermoregulatory responses of the rhesus monkey before and after heat and cold acclimation. These types of studies should provide a data base upon which to evaluate temperature regulation studies, which cannot be directly performed on man.

Only a comprehensive understanding of the biochemical reactions underlying the process of skin renewal will allow scientists to investigate the numerous disorders which involve epidermis, hair, and nails. Howard P. Baden, M.D., Professor of Dermatology at the Massachusetts General Hospital, is receiving grant support to pursue this major objective. Included are studies of genetic disorders of skin in which ichthyosis-like changes in the skin have been associated with deafness and corneal changes in the eyes. Dr. Baden's investigation into the structural proteins of skin hopefully will contribute to the understanding of tissue differentiation that plays a role in ichthyosis-like diseases.



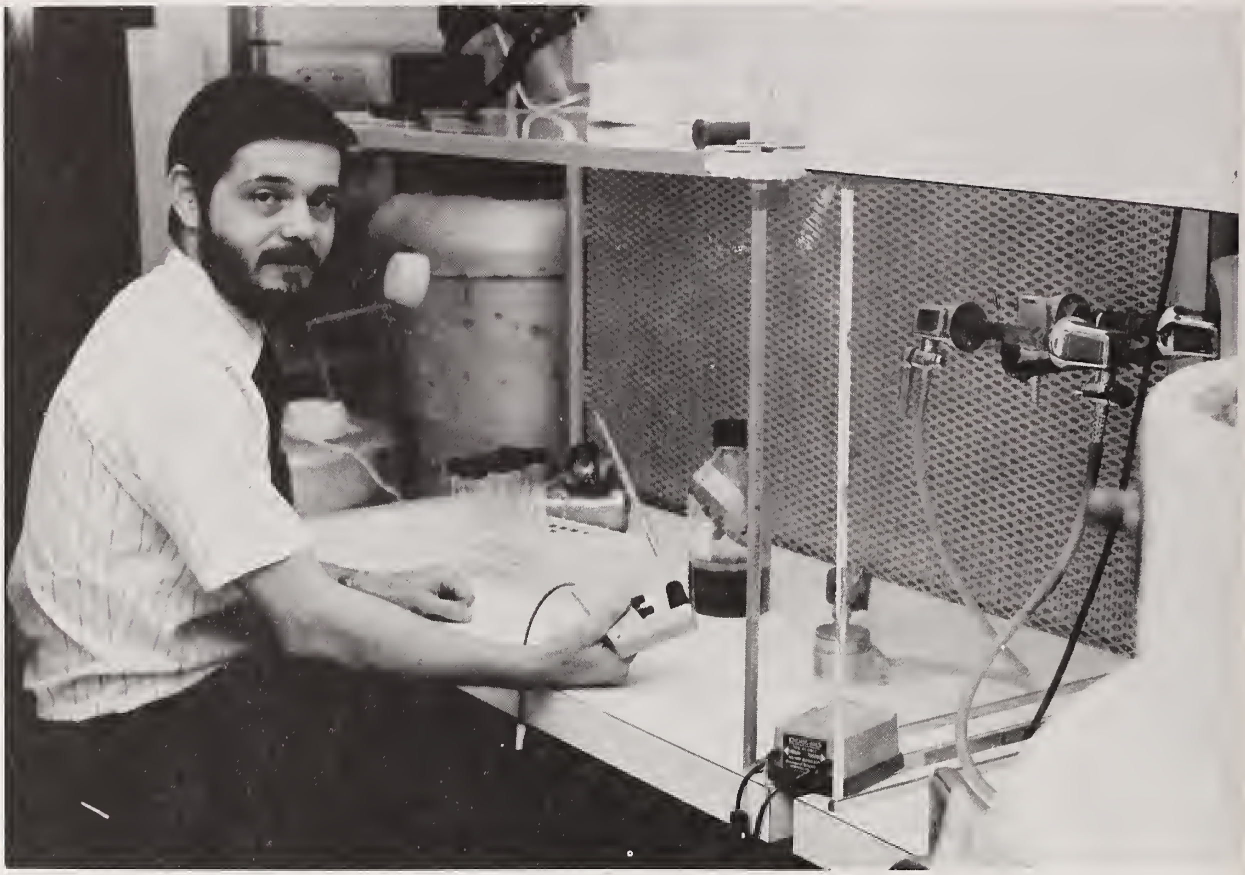
Lowell A. Goldsmith, M.D., Associate Professor of Medicine in the Department of Dermatology at Duke University School of Medicine, is an NIAMDD Research Career Development Award recipient. Dr. Goldsmith's research-supported studies are directed at the isolation and characterization of proteins that appear to be defective in inherited and acquired diseases of the skin. In addition to his particular interest in the biochemical aspects of hair analysis used for detection of malnutrition and other clinical disease states, Dr. Goldsmith is also carrying out clinical studies of new topical agents developed for the removal of the thick scales that characterize diseases such as psoriasis and ichthyosis.

Leonard C. Harber, M.D., has established research laboratories in molecular photochemistry, biophysics, and clinical photobiology at the Columbia University College of Physicians and Surgeons, where he serves as Professor and Chairman of the Department of Dermatology. In addition to his current research projects that include qualitative and quantitative evaluation of photobiologic and environmental factors in skin disease, Dr. Harber directs a research training program for scientists interested in learning photobiologic and biophysical techniques applicable to dermatology.



NIAMDD-supported research projects continue to gain additional insight into the pathophysiologic mechanisms which may relate abnormalities of porphyrin metabolism to cutaneous photosensitivity. Maureen B. Poh, M.D., Assistant Professor of Dermatology at the Columbia University College of Physicians & Surgeons, is utilizing immunohistochemical techniques for localizing tissue porphyrin-binding proteins. She is also in the process of determining distribution of plasma and erythrocyte porphyrin levels in photosensitive patients before and during therapy with a new photoprotective agent, beta-carotene. To complement her NIH-supported research, Dr. Poh-in conjunction with the National Program for Dermatology-is conducting a national screening program for erythropoietic protoporphyria.

In his laboratory in the new Bellevue Hospital building at the New York University Medical Center, Victor R. Wheatley, Ph.D., D.Sc., is examining acrylamide gels of the lipoproteins of sebaceous cells. Dr. Wheatley, Associate Professor of Experimental Dermatology, and his coworkers, have been able to show that contrary to current beliefs, the material accumulating in certain portions of the sebaceous cell is not lipid but a lipid-protein complex. The formation and fate of this complex is one aspect of ongoing studies which may provide new information on the etiology of acne.



Eugene A. Bauer, M.D., is a member of the Division of Dermatology in the Washington University School of Medicine, St. Louis. He is the recipient of an NIAMDD Research Career Development Award. Prior to this award, Dr. Bauer served as a postdoctoral fellow on the NIH training grant awarded to Washington University for support of promising young scientists. Dr. Bauer is actively engaged in the study of factors regulating the synthesis and activity of human skin collagenase in fibroblast cultures. These investigations are particularly directed at elucidating the relationship of this enzyme to recessive dystrophic epidermolysis bullosa, a serious blistering disease of the skin.

George F. Odland, M.D., is Professor of Medicine and Biological Structure in the Division of Dermatology at the University of Washington School of Medicine in Seattle. As Head of Dermatology and a former member of the Institute's National Advisory Council, Dr. Odland has a particular interest in encouraging interdisciplinary programs for basic research in problems of skin biology and pathology. Dr. Odland's personal contributions through grant-supported research have dealt with ultrastructural studies of normal and abnormal cells in the human epidermis.

Eugene M. Farber, M.D., is Professor and Chairman of the Department of Dermatology at Stanford University. The NIAMDD provides research support for Dr. Farber and his coworkers at the University, which is one of the major research and treatment centers for psoriasis. Dr. Farber's current research activities are aimed at clarifying the nature of the processes leading to regression of psoriasis during psoralen-long wave ultraviolet light treatment, a new therapy for extensive psoriasis.

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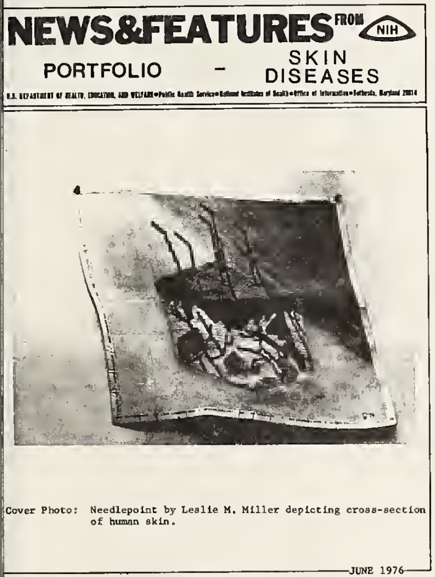

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Cover Photo: Needlepoint by Leslie M. Miller depicting cross-section of human skin.

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